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Direct Healthcare Professional Communication

The content of this communication has been agreed with the Committee for Medicinal Products for Human Use (CHMP) and Irish Medicines Board

10th June 2013

Dear Healthcare Professional:

In agreement with the European Medicines Agency and Irish Medicines Board, Celgene Europe Ltd. would like to inform you about important aspects in the clinical use of Revlimid® (lenalidomide) which has recently been approved for:

- the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Revlimid® (lenalidomide) is also approved for:

- the treatment in combination with dexamethasone of multiple myeloma patients who have received at least one previous therapy.

Risk Management plan

Given the teratogenic risk of Revlimid and its safety profile (i.e. myelosuppression, thrombo-embolic events, risk of progression to AML) risk minimisation measures were requested by health authorities and these are ongoing. These include in particular a pregnancy prevention plan, activities to monitor risks associated with Revlimid® and dissemination of information and education materials to health care professionals (HCP) and patients.

Progression to acute myeloid leukemia in low- and int-1-risk MDS

- A clinical trial showed an increased risk of progression to AML in patients who are transfusion dependant and had complex cytogenetics at baseline compared with patients who had an isolated Del (5q) abnormality. The estimated 2-year cumulative risk of progression to AML was 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype. The benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown. Treatment with Revlimid is therefore limited to patients with an isolated deletion 5q cytogenetic abnormality without additional cytogenetic abnormalities who are considered to be at lower risk for progression to AML.

To gather safety data on the use of Revlimid® in MDS patients, a post authorisation safety study (PASS) has been agreed with CHMP. Specific safety concerns include the progression to AML and risk factors associated with this progression. The intention is that enrolment into the PASS should be completed in parallel to the first prescription of lenalidomide for MDS. The implementation of the PASS is currently under discussion with the Irish Medicines Board and further information will be provided to Healthcare Professionals regarding details of enrolment of patients in this study.

Pregnancy Prevention Programme

Lenalidomide is structurally related to thalidomide which is a known human teratogenic active substance. An embryofoetal development study in animals indicated that lenalidomide produced malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study. These results show that lenalidomide is teratogenic in animals, in a similar way to thalidomide, and is expected to be teratogenic in humans.

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.

We wish to draw your attention to the conditions of the Pregnancy Prevention Programme that must be complied with in this specific patient population.

All women of childbearing potential must:

- Receive counselling regarding the expected teratogenicity of lenalidomide and the need to avoid pregnancy
- Use one effective method of contraception for 4 weeks before therapy, during therapy, during any dose interruptions and for 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 for 4 weeks after the end of therapy. This requirement includes women of childbearing potential who practise absolute and continued abstinence.
- 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 SmPC provides further guidance on the definition of a woman of childbearing potential, counselling, effective contraception and pregnancy testing.

The SmPC can be found on the Medicines Information Online website: www.medicines.ie or alternatively please contact Celgene Medical Information for a print copy of the SmPC at:
Celgene Medical Information
Telephone: 1800 333 111
Fax: 1800 333 112
Email: medinfo.uk.ire@celgene.com

Further information on the Pregnancy Prevention Programme for Healthcare Professionals and patients can be found in the Revlimid® Healthcare Professional's Information Pack, the content of this pack includes:

- Educational Healthcare Professional Brochure
- Educational Brochure for Patients for PPP Information (Males, WCBP, WNCBP)
- Patient Consent Form
- Patient PPP Assessment Algorithm
- Prescription Authorisation Form
- HCP Checklist
- Patient Pocket Information Card
- Pharmacy Registration form
- Physician Registration Form
- Details on the MDS PASS emphasizing that prior to prescribing Revlimid, the healthcare professionals should enrol MDS patients into the PASS

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 any pregnancies that may occur. Please report any confirmed and suspected cases of pregnancy (including exposure to a patient's partner) immediately to:

Celgene Drug Safety
Telephone: 1800 936 217
Fax: 1800 936 477
Email: drugsafetyuk@celgene.com

The Celgene Pregnancy Reporting Form can be found in the Revlimid® Healthcare Professional Information Pack and on www.celgene.ie.

Men
Lenalidomide is excreted into semen. M**ale patients should therefore use condoms** (even if the man has had a vasectomy) throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception.

If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.
You are also requested to notify Celgene Ltd of any pregnancies that may occur. Please report any confirmed and suspected cases of pregnancy (including exposure to a patient's partner) immediately to:

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Telephone: 1800 936 217
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The Celgene Pregnancy Reporting Form can be found in the Revlimid® Healthcare Professional Information Pack and on www.celgene.ie.

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

Patients should not donate blood 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 and differential count, platelet count, haemoglobin and haematocrit levels should be performed at baseline and every week for the first 8 weeks of treatment and then monthly thereafter.
Guidance on dose reduction is provided in Section 4.2 of the attached SmPC.

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

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

In patients with multiple myeloma
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 0.0% in placebo/dexamethasone patients.

In patients with myelodysplastic syndromes

In a phase III clinical study in patients with MDS, lenalidomide was associated with a higher incidence of grade 3 or 4 neutropenia compared with placebo (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo).

Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% of patients on placebo. Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo).

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide and dexamethasone is associated with an increased risk of venous and arterial thromboembolism (predominantly deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident).

A review of arterial thromboembolic events (ATEEs) in the Celgene Pharmacovigilance database through 26 December 2009, showed a total of 493 medically confirmed reports of ATEE. The overall reporting rate for ATEEs was 0.5% with most ATEEs referring to cardiac events (65.7%, mainly myocardial infarctions with 319 reports). A causal relationship between lenalidomide and ATEEs can therefore not be excluded. However, possible explanations and predisposing factors remain to be determined, and the mechanisms involved in the physiopathology of myocardial infarctions remain unknown.

The use of thromboprophylaxis was not documented in the majority of patients with ATEEs (>60%) and venous TEEs (>80%) while risk factors were identified in most patients with a medically confirmed thromboembolic event.

In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma.

Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. **If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started.** Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose, dependent on a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Section 4.4 of the Revlimid SmPC provides further information on specific risks with lenalidomide. The SmPC can be found on the Medicines Information Online website: www.medicines.ie or alternatively please contact Celgene Medical Information for a print copy of the SmPC at:

Celgene Medical Information
Telephone: 1800 333 111
Fax: 1800 333 112
Email: medinfo.uk.ire@celgene.com

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 SmPC.

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.

Tumour Lysis Syndrome
Because lenalidomide has antineoplastic activity tumour lysis syndrome may occur. **The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.**

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. **Patients who had previous allergic reactions while treated with thalidomide should be monitored closely**, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe Skin Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported**. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide**.

Hepatic Disorders

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure and cholestasis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis and toxic hepatitis. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver-enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. **Once parameters have returned to baseline, treatment at a lower dose may be considered.**

Lenalidomide is excreted by the kidneys. **It is important to adjust doses in patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended**, particularly when there is a history of, or concurrent, viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

Second primary malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of SPM has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of acute myeloid leukaemia (AML), MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and autologous stem cell transplantation (ASCT); cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Blood donation
Patient should not donate blood during treatment and for one week after cessation of treatment with Revlimid.

Call for reporting
Please report suspected adverse reactions with any medicine or vaccine to the IMB through:

- **Online Reporting via the IMB Website** www.imb.ie
- **Using downloadable form from the IMB website**. A paper adverse reaction form can be downloaded from the IMB Website. This can be sent by Freepost to the IMB.
- **Using post-paid Report Cards (Yellow Cards).** A supply of cards can be ordered from the IMB: Tel: (01) 6764971, email imbpharmacovigilance@imb.ie
- By telephoning the Pharmacovigilance Section of the IMB, 01- 6764971

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

Adverse reactions associated with the use of Revlimid® should also be reported to Celgene:

Celgene Drug Safety
Celgene Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB

Telephone: 1800 936 217
Fax: 1800 936 477
Email: drugsafetyuk@celgene.com

Company Contact Point

If you have any further questions, require further information, require a print copy of the SmPC or would like to request a Educational Healthcare Professional Kit for Revlimid®, please contact your local Celgene representative at:

Celgene Medical Information
Celgene Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB

Telephone: 1800 333 111
Fax: 1800 333 112
Email: medinfo.uk.ire@celgene.com

Yours faithfully,

Dr David P. Gillen
Medical Director, UK and Ireland
Celgene Limited

A copy of the Revlimid Summary of Product Characteristics is available on the Medicines Information Online website (www.medicines.ie)