Revlimid® (lenalidomide)

Information for Healthcare Professionals

Brochure

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

INTRODUCTION

This Brochure contains the information needed for prescribing and dispensing Revlimid® (lenalidomide), including information about the Pregnancy Prevention Programme (PPP). Please also refer to the Summary of Product Characteristics (SmPC) for further information.

Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

AND

Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant

AND

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy

AND

Revlimid as monotherapy is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

AND

Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

POSOLOGY

Newly diagnosed multiple myeloma

Lenalidomide maintenance in patients who have undergone ASCT

- The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on Days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated. Dose reduction steps are provided in Section 4.2 of the SmPC.

Lenalidomide in combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone until disease progression in patients who are not eligible for transplant

- The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1 to 14 of each 21-day cycle in combination with bortezomib and dexamethasone. The recommended dose of bortezomib is 1.3 mg/m2 body surface area subcutaneously twice weekly on Days 1, 4, 8 and 11 of each 21-day cycle. Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended. Continue lenalidomide 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity. Dose reduction steps are provided in Section 4.2 of the SmPC.

Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant

- The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone,10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dose reduction steps are provided in Section 4.2 of the SmPC.

Multiple myeloma patients with at least one prior therapy

- The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient. Dose reduction steps are provided in Section 4.2 of the SmPC.

Myelodysplastic syndromes

- The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dose reduction steps are provided in Section 4.2 of the SmPC.

Mantle cell lymphoma

- The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles. Dose reduction steps are provided in Section 4.2 of the SmPC.

RISKS OF LENALIDOMIDE

The following section contains advice to Healthcare Professionals about how to minimise the main risks associated with the use of lenalidomide. Please refer also to SmPC (Section 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

Tumour flare reaction

Tumour flare reaction (TFR) has commonly been observed in patients with mantle cell lymphoma, who were treated with lenalidomide. The patients at risk of TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation and appropriate precautions taken.

Lenalidomide may be continued in patients with Grade 1 or 2 TFR without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

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 person-years) compared to controls (1.38 per 100 person-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 patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In newly diagnosed multiple myeloma patients receiving lenalidomide in combination with bortezomib and dexamethasone, the hematologic SPM incidence rate was 0.00 – 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 – 1.04 per 100 person-years.

The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterised, it should be kept in mind when considering and using Revlimid® in this setting.

The incidence rate of haematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not exposed to lenalidomide after ASCT).

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid® either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

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

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of lenalidomide when MDS is associated with Del (5q) and complex cytogenetics is unknown.

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML).

In a post-hoc analysis of a clinical trial of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038).

Progression to other malignancies in mantle cell lymphoma

In mantle cell lymphoma, AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are potential risks.

PREGNANCY PREVENTION PROGRAMME

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4mg/kg/day. Findings from this study showed that lenalidomide produced external malformations (short limbs, bent fingers/toes, wrist and/or tail, supernumerary or absent fingers/toes) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study. For further information regarding study CC-5013-TOX-004, please refer to SmPC, *5.3 Preclinical safety data.*

- If lenalidomide is taken during pregnancy, a teratogenic effect can be expected. Therefore lenalidomide is contraindicated in pregnancy and in women of child bearing potential unless the conditions of the Pregnancy Prevention Programme are met.

- It is a requirement of the Pregnancy Prevention Programme that all Healthcare Professionals ensure that they have read and understood this brochure before prescribing or dispensing lenalidomide for any patient.

- All men and all women of childbearing potential should undergo, at treatment initiation, counselling of the need to avoid pregnancy. Treatment Initiation Forms are provided for this purpose with this Kit. These forms should be signed by both physician and patient; one copy retained by the patient and the other being retained in the patients records.

- Patients should be capable of complying with the requirements of safe use of lenalidomide.

- Patients must be provided with appropriate patient educational brochure and a copy of the Treatment Initiation Form.

- The description of the Pregnancy Prevention Programme and the categorisation of patients based on sex and childbearing potential is set out in the attached Algorithm.

PRESCRIBING LENALIDOMIDE

Women of Childbearing Potential:

- Prescriptions for women of childbearing potential can be for a maximum duration of 4 consecutive weeks according to the approved indications dosing regimens (posology).
- Do not dispense to a woman of childbearing potential unless the pregnancy test is negative and was performed within 3 days of the prescription.
- For those patients who are women of childbearing potential, prescriptions should be limited to one month supply. Dispensing of lenalidomide to women of childbearing potential should only occur within a maximum of 7 days of either the prescription date or the last pregnancy test date, whichever comes first.

All Other Patients:

- For all other patients, prescriptions of lenalidomide should be limited to a maximum duration of 12 consecutive weeks and continuation of treatment requires a new prescription.

Female Patients:

Determine if a woman is not of childbearing potential.

- The following are considered to not have childbearing potential.
  - Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy or during breastfeeding does not rule out childbearing potential).
  - Confirmed premature ovarian failure if confirmed by a specialist gynaecologist.
  - Previous bilateral salpingo-oophorectomy, or hysterectomy
  - XY genotype, Turner's syndrome, uterine agenesis.

You are advised to refer your patient for a gynaecological opinion if you are unsure whether or not she meets these criteria.

PPP Advice for Women of Childbearing Potential

Women of childbearing potential must never take lenalidomide if:

- Pregnant
- Breastfeeding
- A woman who is able to become pregnant, even if not planning to become pregnant, unless all of the conditions of the Pregnancy Prevention Programme are met.

In view of the expected teratogenic risk of lenalidomide, foetal exposure should be avoided

- Women of childbearing potential (even if they have amenorrhoea) must:

- Use at least one effective method of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after lenalidomide therapy, and even in case of dose interruption or
- commit to absolute and continuous abstinence confirmed on a monthly basis

AND

- have a medically supervised negative pregnancy test (with a minimum sensitivity of 25m IU/mL) once she has been established on contraception for at least 4 weeks, at least every 4 weeks during therapy (this includes dose interruptions) and at least 4 weeks after the end of therapy (unless confirmed tubal sterilisation). This includes those women of childbearing potential who confirm absolute and continuous sexual abstinence.

- Patients should be advised to inform the physician prescribing her contraception about the lenalidomide treatment.

- Patients should be advised to inform you if a change or stop of method of contraception is needed.

If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable 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
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Insertion of copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Your patient should be advised that if a pregnancy does occur whilst she is receiving lenalidomide, she must stop treatment immediately and inform her physician immediately.

PPP Advice for Men

- In view of the expected teratogenic risk of lenalidomide, foetal exposure should be avoided
- Inform your patient which are the effective contraceptive methods that his female partner can use.
- Lenalidomide is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for at least 7 days after cessation of treatment if their partner is pregnant or of childbearing potential who is not using effective contraception and even if the male patient has undergone vasectomy.
- Patients should be instructed that if their partner becomes pregnant whilst he is taking lenalidomide or shortly after he has stopped taking Revlimid® he should inform his treating doctor immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice.
- Male patients should not donate semen or sperm during treatment, including during dose interruptions and for 7 days following discontinuation of Revlimid®.

Disposal of unwanted medicine and other handling

- Capsules should not be opened or crushed. If powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.
- Patients should be advised never to give lenalidomide to another person and to return any unused capsules to their pharmacist at the end of the treatment for safe disposal.

Blood donation

Patients should not donate blood during treatment and for at least 7 days after cessation of treatment with lenalidomide.

Requirements in the event of a suspected pregnancy

- Stop treatment immediately, if female patient.
- Refer patient to a physician specialised or experienced in teratology for evaluation and advice.
- Notify AM Mangion Ltd of all such occurrences
  - Pregnancy Capture Form is included in this pack
  - AM Mangion Ltd.
    Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
    Tel: +356 23976333
    Fax: +356 239 76123
    Email: pv@ammangion.com
  - AM Mangion Ltd will wish to follow-up with you the progress of all suspected pregnancies in female patients or partners of male patient cases.

TREATMENT FOR A WOMAN OF CHILDBEARING POTENTIAL CANNOT START UNTIL PATIENT IS ESTABLISHED ON AT LEAST ONE EFFECTIVE METHOD OF CONTRACEPTION FOR AT LEAST 4 WEEKS OR COMMITS TO COMPLETE AND CONTINUED ABSTINENCE AND PREGNANCY TEST IS NEGATIVE!

REPORTING OF ADVERSE REACTIONS

Suspected adverse reactions and medication errors should be reported at
ADR Reporting, The Medicines Authority, Post-Licensing Directorate,
Sir Temi Zammit Buildings, Malta Life Sciences Park,
San Gwann SGN 3000, Malta

Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

OR

ADR Reporting: www.medicinesauthority.gov.mt/adrportal

Communication of Safety Information to other Physicians

It is important that other physicians, for example the patient's general practitioner, who may care for the patient for other conditions are aware of the potential risks of lenalidomide. To assist in this communication, the pack includes a template letter to other treating physicians containing the key safety information for lenalidomide. This wording can be used in communications and between you and other physicians involved in the patient care.

Distribution mechanism for lenalidomide supply

Celgene has implemented a controlled distribution system in order to ensure prevention of foetal exposure to lenalidomide. Prior to treating a patient with lenalidomide, it is required that the treating physician and the patient sign a Treatment Initiation Form to confirm that the benefits and risks of lenalidomide therapy have been explained and understood and that the requirements of the Pregnancy Prevention Programme will be complied with. One copy of this form should be given to the patient and the other should be retained in the patient file. In addition, patients should be provided with the relevant patient information booklet in Maltese or English.

Patient Cards to document childbearing status are contained within the Healthcare Professional Kit. The Patient Cards must be signed to confirm counselling has taken place. For women of childbearing potential, the Patient Card will also document the date and results of the monthly pregnancy test. The Patient Card must be completed and a copy provided to the patient. The pharmacist will be required to verify the correct completion of the patient card for each female patient prior to each dispense of lenalidomide.

CONTACT DETAILS

For information and questions on the risk management of Celgene's products, and the Pregnancy Prevention Programme,

AM Mangion Ltd.
Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
Tel : +356 23976333
Fax: +356 239 76123
Email :pv@ammangion.com

Description of the Pregnancy Prevention Programme and Patient Categorisation Algorithm