Revlimid® (lenalidomide)

Information for Healthcare Professionals

Guide

▼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.

AND

Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

When lenalidomide is given in combination with other medicinal products, the corresponding SmPC must be consulted prior to initiation of treatment.

POSOLOGY

Newly diagnosed multiple myeloma

Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (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.

Follicular lymphoma

- The recommended starting dose of lenalidomide is 20 mg orally once daily on Days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m2 intravenously every week in Cycle 1 (Days 1, 8, 15, and 22) and Day 1 of every 28-day cycle for Cycles 2 through 5. 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 in mantle cell lymphoma and follicular lymphoma patients

Tumour flare reaction has commonly been observed in patients with mantle cell lymphoma, who were treated with lenalidomide or follicular lymphoma treated with lenalidomide and rituximab. 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.

At the physician's discretion, lenalidomide may be continued in patients with Grade 1 or 2 TFR without interruption or modification. At the physician's discretion, therapy with non-steriodal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤ Grade 1, restart lenalidomide treatment at the same dose level for the rest of the cycle.

Patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

Second primary malignancies

The risk of occurrence of second primary malignancies (SPM) must be taken into account before initiating treatment with lenalidomide 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.

An increase of SPM has been observed in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Cases of haematological SPM such as acute myeloid leukaemia (AML) have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with melphalan or immediately following high dose melphalan and ASCT (HDM/ASCT; see Section 4.4 of the SmPC). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with dexamethasone compared to thalidomide in combination with melphalan and prednisone.

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

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see Section 4.4 of the SmPC).

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
- 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®.

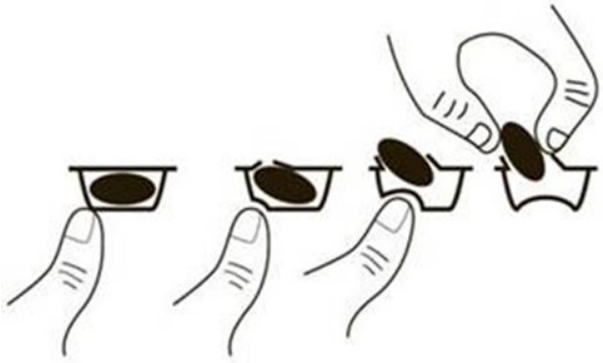
POINTS TO CONSIDER FOR HANDLING THE MEDICINAL PRODUCT: FOR HEALTHCARE PROFESSIONALS AND CAREGIVERS

Keep the blisters with the capsules in the original pack.

Capsules can occasionally become damaged when pressing them out of the blister, especially when the pressure is put onto the middle of the capsule. Capsules should not be pressed out of the blister by putting pressure on the middle nor by putting pressure on both ends as this can result in deformation and breaking of the capsule.

It is recommended to press only on one site at the end of the capsule (see figure below) as therefore the pressure is located to one site only which reduces the risk of capsule deformation or breakage.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule. Refer below for further guidance.



When handling the medicinal product use the following precautions to prevent potential exposure if you are a healthcare professional or caregiver

- If you are a woman who is pregnant or suspect that you may be pregnant, you should not handle the blister or capsule.
- Wear disposable gloves when handling product and/or packaging (i.e. blister or capsule).
- Use proper technique when removing gloves to prevent potential skin exposure (see below).
- Place gloves in sealable plastic polyethylene bag and dispose according to local requirements.
- Wash hands thoroughly with soap and water after removing gloves.If a drug product package appears visibly damaged, use the following extra precautions to prevent exposure
- If outer carton is visibly damaged – **Do Not Open**.
- If blister strips are damaged or leaking or capsules are noted to be damaged or leaking – **Close Outer Carton Immediately**.
- Place the product inside a sealable plastic polyethylene bag.
- Return unused pack to the pharmacist for safe disposal as soon as possible.

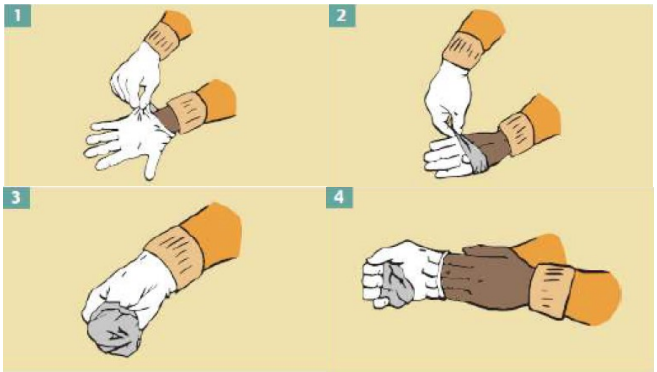
If product is released or spilled, take proper precautions to minimise exposure by using appropriate personal protection

- If capsules are crushed or broken, dust containing drug substance may be released. Avoid dispersing the powder and avoid breathing the powder.
- Wear disposable gloves to clean up the powder.
- Place a damp cloth or towel over the powder area to minimise entry of powder into the air. Add excess liquid to allow the material to enter solution. After handling, clean the area thoroughly with soap and water and dry it.
- Place all contaminated materials including damp cloth or towel and the gloves into a sealable polyethylene plastic bag and dispose in accordance to local requirements for medicinal products.
- Wash your hands thoroughly with soap and water after removing the gloves.
- Please report to Bristol Myers Squibb through its representative AM Mangion Ltd at *pv@ammangion.com*.

If the contents of the capsule are attached to the skin or mucous membranes

- If you touch the drug powder, please wash exposed area thoroughly with running water and soap.
- If your eye had contact with the powder, if worn and if easy to do, remove contact lenses and discard them. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs please contact an ophthalmologist.

Proper Technique for Removing Gloves



- Grasp outside edge near wrist (1).
- Peel away from hand, turning glove inside-out (2).
- Hold in opposite gloved hand (3).

- Slide ungloved finger under the wrist of the remaining glove, be careful not to touch the outside of the glove (4).
- Peel off from inside, creating a bag for both gloves.
- Discard in appropriate container.
- Wash your hands with soap and water thoroughly.

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

AND

AM Mangion Ltd
Mangion House
New Street off Valletta Road
Luqa LQA6000, Malta
Email: pv@ammangion.com T
Tel – 00 356 23976333

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

Bristol Myers Squibb 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.
The treating Physician will need to provide patients with appropriate **Patient Educational Guide** and patient card.
This Material is a condition to the Marketing Authorization, and it has been approved by the Medicines Authority on [25/02/2021]

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 Bristol Myers Squibb'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

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG

Description of the Pregnancy Prevention Programme and Patient Categorisation Algorithm