• PREGNANCY PREVENTION PROGRAM •

HEALTHCARE PROFESSIONALS BROCHURE
FOR IMMUNOMODULATORY AGENTS

Revlimid® (Lenalidomide) and Pomalyst® (Pomalidomide)

Bristol Myers Squibb™

Pomalyst® (pomalidomide) capsules

Revlimid® (lenalidomide) capsules

HEALTHCARE PROFESSIONALS BROCHURE FOR LENALIDOMIDE AND POMALIDOMIDE

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INTRODUCTION

This brochure contains safety information for healthcare professionals on the teratogenic risk of the immunomodulatory agents lenalidomide and pomalidomide, as well as the requirements for prescribing and dispensing these immunomodulatory agents under the Pregnancy Prevention Program (PPP) to ensure safe use and handling of the products. This brochure also contains information on other risks associated with the use of these immunomodulatory agents. Please refer to the Revlimid® Package Insert or Pomalyst® Package Insert for the full safety and prescribing information.

THE PREGNANCY PREVENTION PROGRAM AT A GLANCE

Healthcare professionals must:

- Communicate the benefits and risks of treatment with lenalidomide and pomalidomide to their patients
- Provide pregnancy prevention counseling per patient risk categorization at treatment initiation
- Perform a pregnancy test (if applicable) prior to each prescription at every 4 weeks
- Issue patient educational materials to patients, as described below
- Remind patients of the safe use of lenalidomide and pomalidomide at each consultation and each time a prescription is dispensed

PREGNANCY PREVENTION PROGRAM

The PPP and educational materials under the program were developed to help healthcare professionals (HCPs) and patients understand the risks of lenalidomide and pomalidomide use during pregnancy. These materials provide a comprehensive overview of how the PPP prevents birth defects and fetal exposure to lenalidomide and pomalidomide.

- Thalidomide is a powerful human teratogen and, if taken during pregnancy, can cause severe birth defects or death to a developing fetus. In the 1950s and 1960s, thalidomide was prescribed to pregnant women as a sedative and to relieve morning sickness. Consequently, approximately 12,000 children were born with severe birth defects caused by thalidomide. Lenalidomide and pomalidomide are structurally related to thalidomide. Lenalidomide induced malformations in monkeys similar to those described with thalidomide, and pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If lenalidomide or pomalidomide are given during pregnancy, a teratogenic effect in humans cannot be ruled out.

- Lenalidomide and pomalidomide are contraindicated in pregnancy, and in female patients of childbearing potential unless all of the conditions of the PPP, as described in this brochure, are met.
- Lenalidomide and pomalidomide can pass into seminal fluid. Male patients must also follow the necessary requirements of the PPP to prevent exposure to a female partner.
- It is a requirement of the PPP that all HCPs ensure that they have read and understood this brochure before prescribing or dispensing lenalidomide and pomalidomide to their patients.
- At treatment initiation, all male patients and all female patients of childbearing potential should undergo counseling about the need to avoid pregnancy. A Risk Awareness Form for Counseling Patients Receiving Immunomodulatory Agents is appended to this document to guide HCPs through the fulfillment of the PPP requirements. Please use the Patient Agreement Form for Immunomodulatory Agents to document patient understanding.
- Healthcare professionals are advised to refer to the Risk Awareness Form for Counseling Patients Receiving Immunomodulatory Agents for more information about ensuring that patients receiving treatment with lenalidomide and pomalidomide are aware of the requirements of the PPP and the steps required for compliance.
- Patients should be capable of complying with the requirements for safe use of lenalidomide or pomalidomide.
- Prior to treatment initiation, patients and HCPs must fill out the
    - Risk Awareness Form for Counseling Patients Receiving Immunomodulatory Agents,
    - Patient Agreement Form for Immunomodulatory Agents, and
    - Patient Medication Guide for Immunomodulatory Agents.

  Patients should be provided with a copy of the
    - Patient Agreement Form for Immunomodulatory Agents, and
    - Patient Medication Guide for Immunomodulatory Agents.

  These materials will provide the relevant information to patients receiving treatment with lenalidomide or pomalidomide.
- The description of the PPP and the categorization of patients based on gender and childbearing potential is described in the algorithm (attached).
- Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications and dosing regimens, and prescriptions for all other patients can be for a maximum duration of 12 weeks.

For more information about prescribing and dispensing lenalidomide and pomalidomide, including the recommended dosing schedule and duration, consult the Revlimid® and Pomalyst® Package Insert, respectively.

Guidance for All Patients

Patients must be informed not to donate blood during treatment (including during dose interruptions) and for at least 7 days after cessation of treatment with lenalidomide and pomalidomide. Any unused medication at the end of treatment must be returned to their pharmacist for safe disposal.

Patients must understand that their treatment is only for them and it:

- Must not be shared with anyone else, even if they have similar symptoms
- Must be stored away safely so that no one else can take the medicine by accident
- Must be kept out of reach of children

Handling Precautions

- The capsules should not be opened, crushed or overly handled.
- If powder from lenalidomide or pomalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water.
- If powder from lenalidomide or pomalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.
- 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.

For more information on safe handling of lenalidomide and pomalidomide, please refer to the Revlimid® and Pomalyst® Package Insert, respectively.

Determining Childbearing Potential

A female patient or a female partner of a male patient is not of childbearing potential if she meets at least one of the following criteria. Please refer the patient for a gynecological opinion if you are uncertain.

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist

- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential.

A female patient must never take lenalidomide or pomalidomide if she is pregnant.

PPP Guidance for Female Patients of Childbearing Potential

In view of the teratogenic risk associated with lenalidomide and pomalidomide, fetal exposure should be avoided.

Prior to treatment, female patients of childbearing potential are required to have a negative pregnancy test and at least 4 weeks of effective contraceptive use or commit to absolute and continuous abstinence from heterosexual intercourse prior to beginning treatment. They must also be informed about the risks and precautions associated with lenalidomide and pomalidomide, including the potential risk of birth defects and the need for pregnancy prevention during and following discontinuation of treatment. Please refer to the Risk Awareness Form for Counseling Patients Receiving Immunomodulatory Agents for additional guidance.

A female patient must never take lenalidomide or pomalidomide if they are able to become pregnant, even if not planning to become pregnant, unless all of the conditions of the PPP are met.

- Female patients of childbearing potential (even if they have amenorrhea or irregular menstrual periods) must:
    - Use at least one effective method of contraception for at least 4 weeks before, during, and until at least 4 weeks after cessation of treatment with lenalidomide or pomalidomide, and even in case of dose interruption, or
    - Commit to absolute and continuous abstinence from heterosexual intercourse during the entire period of teratogenic risk associated with lenalidomide and pomalidomide. The reliability of sexual abstinence needs to be evaluated by the HCP in relation to the duration of use of treatment with lenalidomide or pomalidomide and the preferred and usual lifestyle of the patient and be confirmed on a monthly basis. The HCP should document this each month in the patient's medical records.

    AND

    - Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25 mIU/mL) prior to starting treatment (during the consultation when lenalidomide or pomalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once contraception has been established for at least 4 weeks prior to treatment initiation), at least every 4 weeks during

treatment (including dose interruptions), and at least 4 weeks after the end of treatment (unless confirmed tubal sterilization). This includes female patients of childbearing potential who confirm absolute and continuous abstinence from heterosexual intercourse during the entire period of teratogenic risk associated with lenalidomide and pomalidomide.

- Patients should be advised to inform the HCP prescribing her contraception about her treatment with lenalidomide or pomalidomide.
- Patients should be advised to inform the HCP prescribing her treatment with lenalidomide or pomalidomide if a change or cessation in method of contraception is needed.
- A patient not established on effective contraception must be referred to an appropriately trained HCP for contraceptive advice in order that contraception can be initiated.
- The following methods are examples of effective contraception:
    - implant
    - levonorgestrel-releasing intrauterine system
    - medroxyprogesterone acetate depot
    - tubal sterilization
    - sexual intercourse with a vasectomized 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 or pomalidomide, 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 to 6 weeks after discontinuing combined oral contraception.

Patients should be advised to inform their treating HCP of a missed menstrual period, any unusual menstrual bleeding, or if she believes that she may be pregnant. If a pregnancy does occur while receiving treatment with lenalidomide or pomalidomide, treatment must be discontinued, and the treating HCP informed immediately. Refer the patient to an HCP specialized in teratology for evaluation and advice.

PPP Guidance for Male Patients

In view of the teratogenic risk associated with lenalidomide and pomalidomide, fetal exposure should be avoided.

Prior to treatment, male patients must be informed about the risks and precautions associated with lenalidomide and pomalidomide, including the potential risk of birth defects and the need for pregnancy prevention during and following discontinuation of treatment. Please refer to the Risk Awareness Form for Counseling Patients Receiving Immunomodulatory Agents for additional guidance.

- Lenalidomide and pomalidomide have been detected in seminal fluid. Therefore, all male patients, including those who have had a vasectomy, should use condoms throughout treatment duration, during dose interruptions, and for at least 7 days after cessation of treatment if his partner is pregnant or of childbearing potential and is not using effective contraception (even if the male patient has undergone vasectomy).
- Inform patients which effective contraceptive methods his female partner can use. The following methods are examples of effective contraception: Implant, levonorgestrel-releasing intrauterine system, medroxyprogesterone acetate depot, tubal sterilization, Sexual intercourse with a vasectomized male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation inhibitory progesterone-only pill (i.e. desogestrel).
- Instruct patients that if his partner becomes pregnant while he is on treatment with lenalidomide or pomalidomide or within 7 days after medication has been discontinued, the HCP should be informed immediately. His partner should also inform her HCP immediately. It is recommended that she be referred to an HCP specialized in teratology for evaluation and advice.
- Male patients should not donate semen or sperm during treatment, including during dose interruptions and for at least 7 days following discontinuation of treatment as lenalidomide or pomalidomide can pass into seminal fluid.

In the Event of a Suspected Pregnancy or Exposure of a Pregnant Partner

- If female patient, stop treatment immediately and inform the treating HCP immediately. Refer the patient to a HCP specialized or experienced in teratology for evaluation and advice.
- If male patient, inform treating HCP immediately if female partner becomes pregnant while he is on treatment with lenalidomide or pomalidomide, or within 7 days after he has stopped receiving treatment with lenalidomide or pomalidomide. It is recommended to refer the female partner to a HCP specialized or experienced in teratology for evaluation and advice.

- Notify Bristol Myers Squibb (BMS) of all such occurrences.
    - Email: MedInfo.Singapore@bms.com
    - Phone: 1800 415 5182
- BMS will wish to follow up with you regarding the progress of all suspected pregnancies in female patients or female partners of male patients.

OTHER RISKS ASSOCIATED WITH LENALIDOMIDE OR POMALIDOMIDE

The following section contains advice about how to minimize the other risks associated with the use of Revlimid® (lenalidomide) or Pomalyst® (pomalidomide).

Thrombocytopenia

Thrombocytopenia is one of the most commonly reported blood and lymphatic system disorders with Revlimid® (lenalidomide) and Pomalyst® (pomalidomide). It is recommended to monitor complete blood counts, including platelet count at baseline, weekly for the first 8 weeks and monthly thereafter. Patients should be monitored for signs of bleeding such as epistaxis, especially with use of concomitant medicinal products known to increase the risk of bleeding. The management of thrombocytopenia may require dose modification, use of blood product support and/or growth factors.

Please refer to the respective package insert on the recommended dose modifications during treatment and restart of treatment following an event of thrombocytopenia.

Second primary malignancies

The risk of occurrence of second primary malignancies (SPM) with Revlimid® (lenalidomide) must be considered before initiating treatment with Revlimid® (lenalidomide). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

SPM, such as non-melanoma skin cancer, is also a potential adverse reaction with Pomalyst® (pomalidomide).

Please refer to the respective package insert for further information regarding this adverse reaction.

Cardiac Dysfunction (Failure)

Cardiac dysfunction (failure) may occur during the treatment with Pomalyst® (pomalidomide). Cardiac events, including congestive cardiac failure, have also been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such

patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events.

Cardiac failure is also a potential adverse reaction in patients treated with Revlimid® (lenalidomide).

Please refer to the respective package insert for further information about these adverse reactions and the recommended precautions.

Tumor flare reaction and Tumor lysis syndrome

Cases of tumor flare reaction (TFR) and tumor lysis syndrome (TLS), including fatal cases, have been reported with the use of Revlimid® (lenalidomide). Cases of TLS have also been reported in clinical trials and post-marketing use of Pomalyst® (pomalidomide). The patients at risk of TFR and TLS are those with high tumor burden prior to treatment. Caution should be practiced when introducing these patients to Revlimid® (lenalidomide) or Pomalyst® (pomalidomide). These patients should be monitored closely, and appropriate precautions taken where necessary.

REPORTING OF ADVERSE REACTIONS

The safe use of lenalidomide or pomalidomide is of paramount importance. As part of our ongoing safety monitoring, BMS wishes to be informed of adverse reactions that have occurred during the use of these medicines. Please report any adverse reactions to BMS via:

- Email: MedInfo.Singapore@bms.com
- Phone: 1800 415 5182

You are also encouraged to report any suspected adverse reactions to the Vigilance & Compliance Branch, Health Products Regulation Group, Health Sciences Authority via:

- https://www.hsa.gov.sg/adverse-events
- Phone: 6866 1111

CONTACT DETAILS

For information and questions on the risk management of BMS' products and the PPP, contact

- Email: Safety_Singapore@bms.com

PATIENT RISK CATEGORIZATION, PREGNANCY TEST AND CONTRACEPTION REQUIREMENTS ALGORITHM

Evaluate new patient

Male

Start lenalidomide or pomalidomide. Condom required for sexual intercourse (even if vasectomized) for the duration of treatment, during dose interruptions, and for at least 7 days after treatment discontinuation, if partner is pregnant or of childbearing potential and not using effective contraception.

Female

Not of childbearing potential

At least one criterion must be fulfilled:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential.

Start lenalidomide or pomalidomide. Contraception and pregnancy testing are not required

Of childbearing potential

If not already using effective contraception, start effective contraception at least 4 weeks prior to initiation of treatment, unless practicing absolute and continuous abstinence from heterosexual intercourse.

- *Implant, levonorgestrel-releasing intrauterine system, medroxyprogesterone acetate depot, tubal sterilization, Sexual intercourse with a vasectomized male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation inhibitory progesterone-only pill (i.e. desogestrel)*

Contraception continues during treatment, including dose interruptions, and for at least 4 weeks after treatment discontinuation.

Test for pregnancy after at least 4 weeks of effective contraception (even if sexually abstinent)

Negative

Start lenalidomide or pomalidomide. Test for pregnancy at least every 4 weeks, even if sexually abstinent

Positive

DO NOT START TREATMENT

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