Manual for Healthcare Professionals

PREGNANCY PREVENTION PROGRAM (PPP)

version 1.2

MYOLID® (LENALIDOMIDE)

Before prescribing MYOLID® please consult the full local prescribing information by scanning the following QR code.

Introduction

The Manual:

- is intended for healthcare professionals involved in the treatment of patients with lenalidomide alone or in combination with other medicines.
- is essential to ensure the safe and effective use of lenalidomide and adherence to the Pregnancy Prevention Program (PPP).
- must be read before prescribing and administering lenalidomide.
- is distributed within the educational material package which includes (in addition to the Healthcare Professional Manual):
    - Package Insert
    - Patient Manual
    - Prescriber registration form
    - Patient informed consent
    - Counselling Checklist

SECTION 1

About MYOLID® (LENALIDOMIDE)

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

MYOLID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of previously untreated multiple myeloma patients who are not eligible for transplant.

MYOLID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

Dosing and Administration

MYOLID® (lenalidomide) should only be prescribed by Specialist Physician experienced in the management of malignancies, who have undergone the MYOLID® (lenalidomide) educational programme on Pregnancy Prevention Programme.

Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma (MM).

Please refer to the MYOLID® Package Insert for dose regimens.

SECTION 2

Pregnancy Prevention Program

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. In monkeys, lenalidomide induced malformations like those described with thalidomide (see sections 4.6 and 5.3 of MYOLID® package insert).

A teratogenic effect of lenalidomide is to be expected if taken during pregnancy.

Lenalidomide is therefore contraindicated in pregnancy and while breastfeeding. It is also contraindicated in women of childbearing potential unless all conditions of the Pregnancy Prevention Program (PPP) are met.

The PPP is an integral part of the risk minimisation plan which aims to reduce and prevent the risks associated with the use of lenalidomide.

As required by the PPP, all Healthcare Professionals involved must have read and understood this Manual before prescribing or dispensing lenalidomide to any patient.

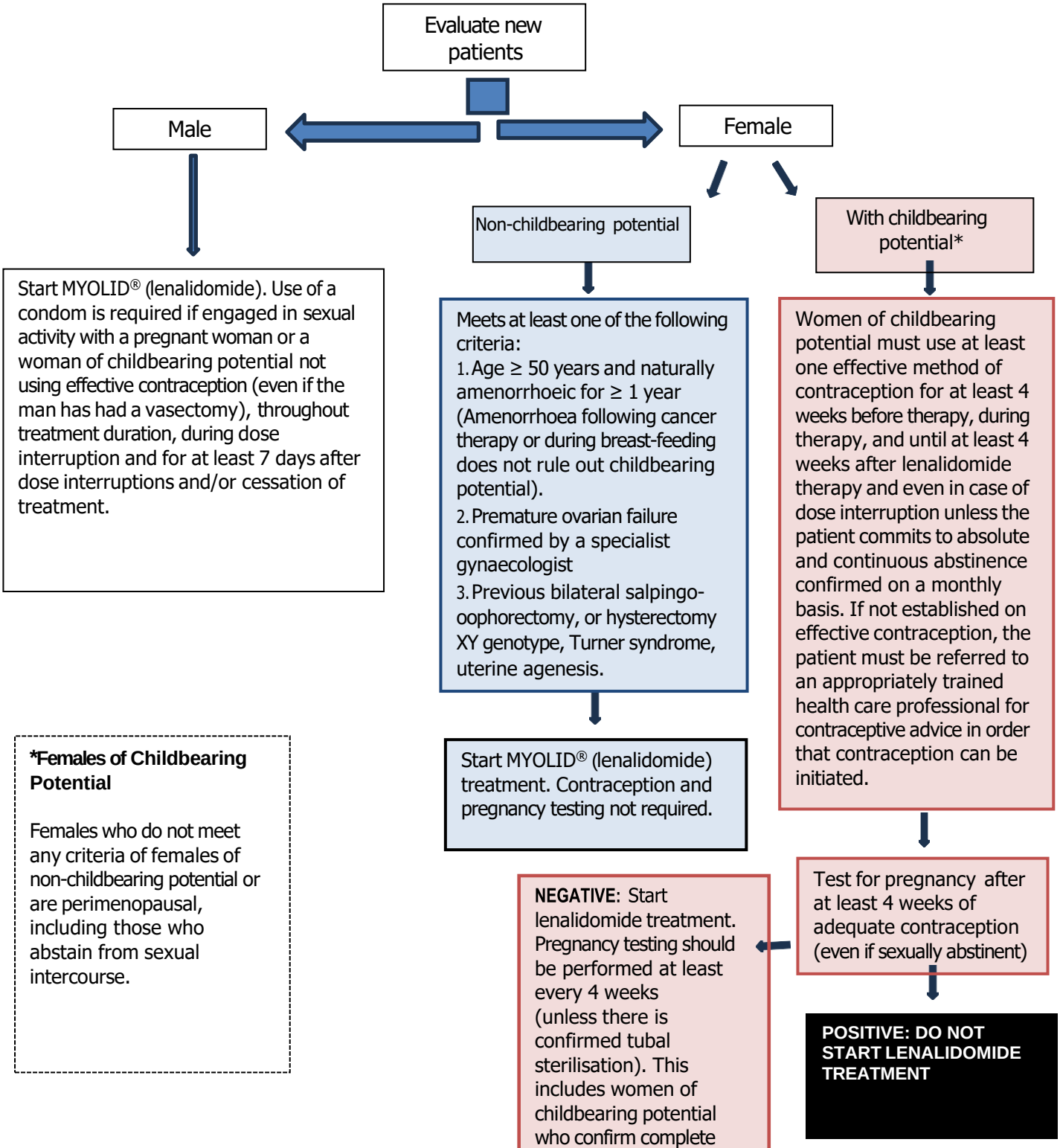
All men and women of childbearing potential must be adequately informed about the need to avoid pregnancy.

All patients should be able to meet the requirements of the PPP for the safe administration of lenalidomide and should be provided with the Patient Manual for the PPP.

The conditions of the PPP must be fulfilled for all patients unless there is reliable evidence that the patient is of non-childbearing potential.

SECTION 3

Classifying Patient Risk Categories



***Females of Childbearing Potential**

Females who do not meet any criteria of females of non-childbearing potential or are perimenopausal, including those who abstain from sexual intercourse.

SECTION 4

Counselling Messages

For women of childbearing potential, lenalidomide is contraindicated unless all the following are met:

- She understands the expected teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment.
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test.
- She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilisation.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

Women of childbearing potential should not take lenalidomide if they have any of the following conditions:

- Pregnant
- Breastfeeding
- A woman who may become pregnant, even if she is not planning to become pregnant, unless all conditions in the Pregnancy Prevention Program are met.

  * The patient should be advised that if she becomes pregnant or suspects she may be pregnant while taking **lenalidomide,** she must stop treatment immediately and inform her doctor.

For male patients taking lenalidomide

Pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2 of Package Insert). As a precaution and considering special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.

- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), throughout treatment duration, during dose interruption and for at least 7 days after dose interruptions and/or cessation of treatment.

- Understand that if his female partner becomes pregnant whilst he is taking MYOLID® or 7 days after he has stopped taking MYOLID®, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

SECTION 5

Contraception and Pregnancy Testing

Women of childbearing potential 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 unless the patient commits to absolute and continuous abstinence confirmed monthly. 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 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)

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.

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.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

SECTION 6

Lenalidomide prescription

Women of childbearing potential

Prescription for women of childbearing potential can be made for up to 4 consecutive weeks according to the dosing regimens for the approved indications.

Do not dispense the drug to a woman of childbearing potential unless she has had a negative pregnancy test within 3 days of prescribing it.

For all other patients

The prescription of lenalidomide for all other patients should be limited to a maximum duration of 12 consecutive weeks of treatment and then a new prescription is required to continue therapy.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment for safe disposal.
Patients should not donate blood during therapy (including during dose interruptions) or for at least 7 days following discontinuation of lenalidomide.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule.

SECTION 7

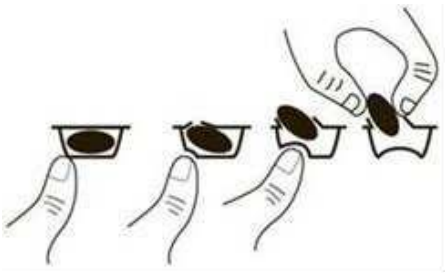
HOW TO HANDLE THE MEDICINAL PRODUCT: ADVICE FOR HEALTHCARE PROVIDERS

Consult the Package Insert for lenalidomide for handling instructions.

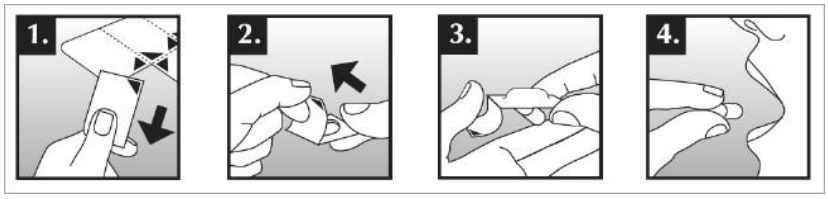
Keep the medicine in the original package and make sure it is not damaged and/or broken when taking it out.

Lenalidomide can come in different types of immediate packaging.

If lenalidomide comes in hard capsules within a non-peelable blister, to extract the capsule, it is recommended to press on only one side at one end of the capsule (see figure below) as the pressure applied in the middle or on both ends at the same time it could determine the deformation and breakage of the capsule itself.



If lenalidomide comes as hard capsules in a peelable blister, to remove the capsule, hold the blister by the edges and separate one end of the blister from the rest of the blister by gently tearing along the perforations around it (1). Lift the edge of the film and peel off the film completely (2). Turn the capsule onto your hand (3). Patients should be advised to swallow the capsule whole, preferably with water (4).



Healthcare professionals should wear disposable gloves when handling the blister or capsule. Gloves should then be carefully removed to prevent skin exposure, placed in a sealable polyethylene bag, and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are known or suspected to be pregnant must not handle the blister or capsule.

Further details are available below.

When handling the medicine, use the following precautions to prevent potential exposure:

- If you are pregnant or think you may be pregnant, you must not handle the blister or capsule.
- Wear disposable gloves when handling the medicine and/or the packaging (e.g. blisters and/or capsules).
- Use proper technique when removing gloves to prevent potential skin exposure (see below).
- Place the gloves in a sealable polyethylene bag and dispose of according to local requirements.
- Wash hands thoroughly with soap and water after removing gloves.

If the drug package appears visibly damaged, use the following additional precautions to prevent exposure:

- If the outer packaging is visibly damaged – **Do not open it.**
- If the blister foils are damaged or cracked or the capsules appear to be damaged or cracked – **Close the outer carton immediately.**
- Place the product inside a sealable polyethylene bag.
- Return the unused pack to your pharmacist as soon as possible to ensure safe disposal.

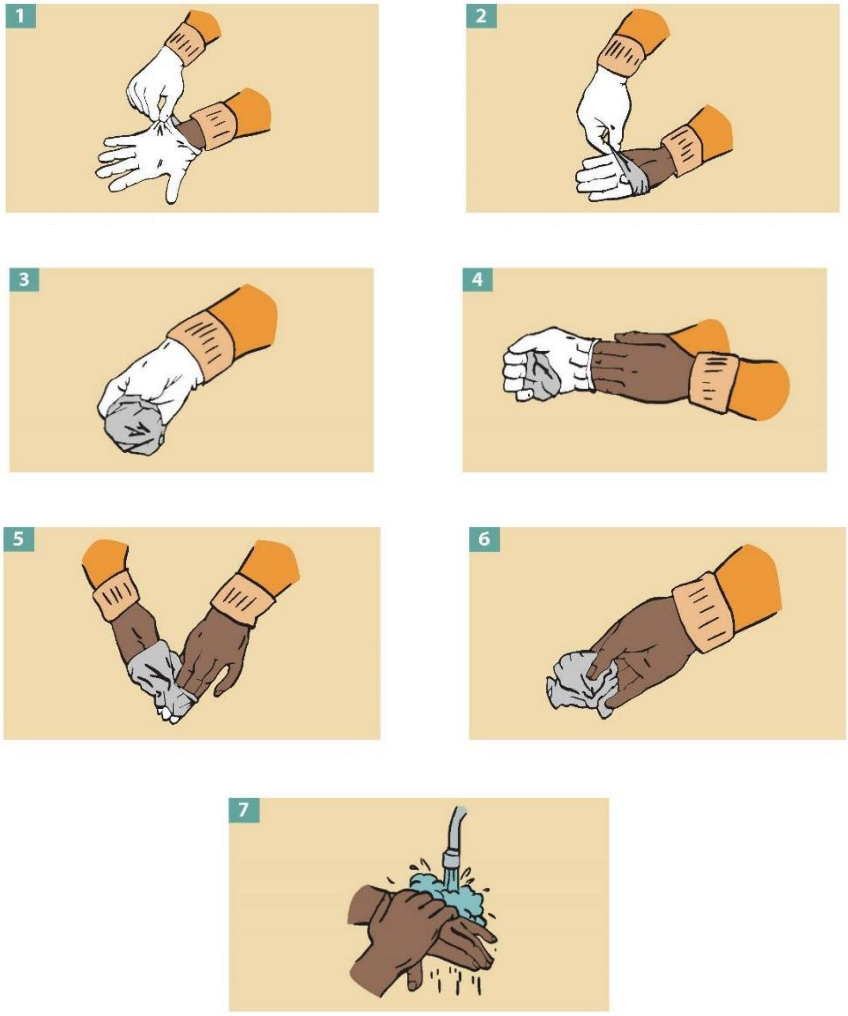
If the product has spilled or leaked, use adequate precautions to minimize possible exposure by adopting personal protection measures:

- If the capsules are crushed or broken, the powder containing the medicinal substance may have leaked out. Avoid dispersing dust and avoid breathing dust.
- Wear disposable gloves to collect the dust.
- Place a damp cloth or tarp over the area where the dust is present to minimize dust kicking into the air. Further wet the cloth to allow the material to enter the solution. Then clean the affected area thoroughly with soap and water and dry it.
- Place all contaminated materials including drape or wet cloth and gloves in a sealable polyethylene bag and dispose of in accordance with local regulations.
- Wash hands thoroughly with soap and water after removing gloves.
- Immediately report what happened to the contacts indicated on the letter accompanying the materials (which can also be reached via the QR Code at the bottom of the same).

If the contents of the capsules come into contact with the skin or mucous membranes:

- If you have come in contact with the drug powder, wash the exposed area thoroughly with soap and running water.
- If the dust gets into your eyes, immediately flush eyes with large amounts of water for at least 15 minutes. If you wear contact lenses, remove the lenses and discard them before flushing your eyes with water. In case of irritation, contact an ophthalmologist.

Proper glove removal technique



- Grasp the outer edge near the wrist (1).
- Remove from the hand by turning the glove inside out (2).
- Hold the removed glove in the hand still wearing the glove (3).
- Slip the fingers of the ungloved hand under the wrist of the other glove, being careful not to touch the outside of the glove (4).
- Remove from the inside, creating a bag that contains both gloves (5).
- Dispose of in a suitable container (6).
- Wash your hands thoroughly with soap and water (7).

SECTION 8

Steps to completing initial and subsequent prescriptions.

FOR THE FIRST PRESCRIPTION MUST MAKE SURE THAT:

- Your patient is fully educated on the risks of lenalidomide.
- Your patient has received information on the safe use of lenalidomide according to the measures described in this manual and in the Package Insert .
- Lenalidomide is prescribed in accordance with the measures described in this manual and in the Package Insert.
- The patient is provided with the Patient Manual.
- If the patient is a woman of childbearing age, before issuing each prescription, she must have taken a pregnancy test no more than 3 days before, which must be negative.

MYOLID® PPP Enrollment process

❖ **Prescriber Enrollment in the MYOLID® (lenalidomide) PPP**

· Prescribers must complete the Prescriber Registration Form

· Return the completed form through email to **MYOLID PPP ENROLMENT (vanessa.lacuesta@dksh.com)**

❖ **Pharmacy Enrollment in the MYOLID® (lenalidomide) PPP**

· Pharmacies must provide a list of pharmacists to dispense lenalidomide to be sent to **MYOLID PPP ENROLMENT (vanessa.lacuesta@dksh.com)** upon request. The list will be updated annually.

Instructions for Incompetent Adult Patients

For an incompetent adult patient, an authorized representative must sign the Informed Consent Form:

- An authorized representative is a caretaker authorized under applicable law in the country to consent to treatment on the incompetent patient's behalf
- The authorized representative must read the material, initial the appropriate statements, and agree to ensure compliance by signing and dating the form.

For the Prescriber:

Prescribers must register using the Prescriber Registration Form before prescribing lenalidomide.

- ❖ Obtain a medically supervised negative pregnancy test on the same day of the prescribing visit or in the 3 days prior to the visit to the prescriber prior to writing an initial prescription for lenalidomide even if absolute or continuous abstinence is the chosen method of birth control. The pregnancy test must be sensitive to at least 25 mIU/mL.

- ❖ Prescribers should determine the risk category of the patient and counsel according to this risk category (refer to separate section for all counselling messages).

- ❖ Write and sign prescription and ensure it includes Prescriber name and the duration of treatment according to maximum permitted for the patient's risk category (4 weeks for females with childbearing potential and 12 weeks for all other patients). No automatic refills or telephone prescriptions are permitted.

For the Pharmacist:

Before dispensing lenalidomide:

- ❖ Pharmacist verifies that the prescriber is enrolled and:

a. prescriber name is documented on the prescription
b. duration of treatment prescribed according to maximum permitted for the patient's risk category (4 weeks for females with childbearing potential and 12 weeks for all other patients), and prescription was written within the last seven days.

- ❖ Pharmacist must obtain the Patient Informed Consent Form. Fill out the Informed Consent Form with the patient as directed.

- The form must be completed and signed by both pharmacist and patient. Pharmacist will keep a copy for documentation.
- If the patient is under 21 years of age, his or her legal guardian must read and understand this material prior to the patient signing.

- ❖ Pharmacist should counsel the patient according to his/her risk category (refer to separate section for all counselling messages).

- ❖ Pharmacist dispense the medication to the patient with the Patient Manual. Pharmacists are only able to dispense their institution's prescription.

For females of childbearing potential, prescribers must obtain scheduled medically supervised pregnancy tests every at least 4 weeks, except in case of confirmed tubal sterilization. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

SECTION 9

Other risks associated with the use of lenalidomide

The following section contains guidance for Healthcare Professionals on how to minimize the main risks associated with the use of lenalidomide. For more information about risks associated with lenalidomide, consult the Myolid® Package Insert.

Tumor flare reaction (TFR) and tumour lysis syndrome (TLS)

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. Cases of TLS and tumour flare reaction (TFR), including fatal cases, have been reported (see section 4.8 of Myolid® package insert). The patients at risk of TLS and 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.

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.

The risk of occurrence of hematologic SPM must be considered before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Acute Myeloid Leukemia

Cases of acute myeloid leukaemia have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan/autologous stem cell transplantation. This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

SECTION 10

Reporting of Adverse Event and Pregnancy

As part of the ongoing safety monitoring, DKSH wishes to be informed of all adverse events, including pregnancy events, which have occurred during the use. In the event of pregnancy report, it is important that DKSH should be notified immediately.

Adverse events should be reported to the:

HSA via their online reporting portal (https://www.hsa.gov.sg/adverse-events). Please also email a copy of the submitted HSA adverse event reporting form to hec-pv.sin@dksh.com