Lenalidomide Grindeks
(lenalidomide)

Educational brochure for Healthcare Professionals

INTRODUCTION

Lenalidomide is an immunomodulating medicinal product.

Lenalidomide Grindeks is indicated for the following:

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

AND

- Lenalidomide 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

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

AND

- Lenalidomide 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 of lenalidomide is 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 Dexamethasone until Disease Progression in Patients who are Not Eligible in Transplant

The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. 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 of lenalidomide is 10 mg orally once daily on Days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on Days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on Days 1 to 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 monotherapy as follows: 10 mg orally once daily on Days 1 to 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 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on Days 1 to 4 every 28 days. The prescriber 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.

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 some of 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

Tumor Flare Reaction (TFR) has commonly been observed in patients with mantle cell lymphoma, who were treated with lenalidomide or with 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 practised 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 prescriber's discretion, lenalidomide may be continued in patients with Grade 1 or 2 TFR, without interruption or modification. At the prescriber's discretion, therapy with non-steroidal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In patients with Grade 3 or 4 TFR, withhold treatm ent 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. Prescribers 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 (PPP)

- 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 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.

- If lenalidomide is taken during pregnancy, a teratogenic effect is expected. Therefore, lenalidomide is contraindicated in pregnancy and in women of childbearing potential unless the conditions of the Pregnancy Prevention Program are met.

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

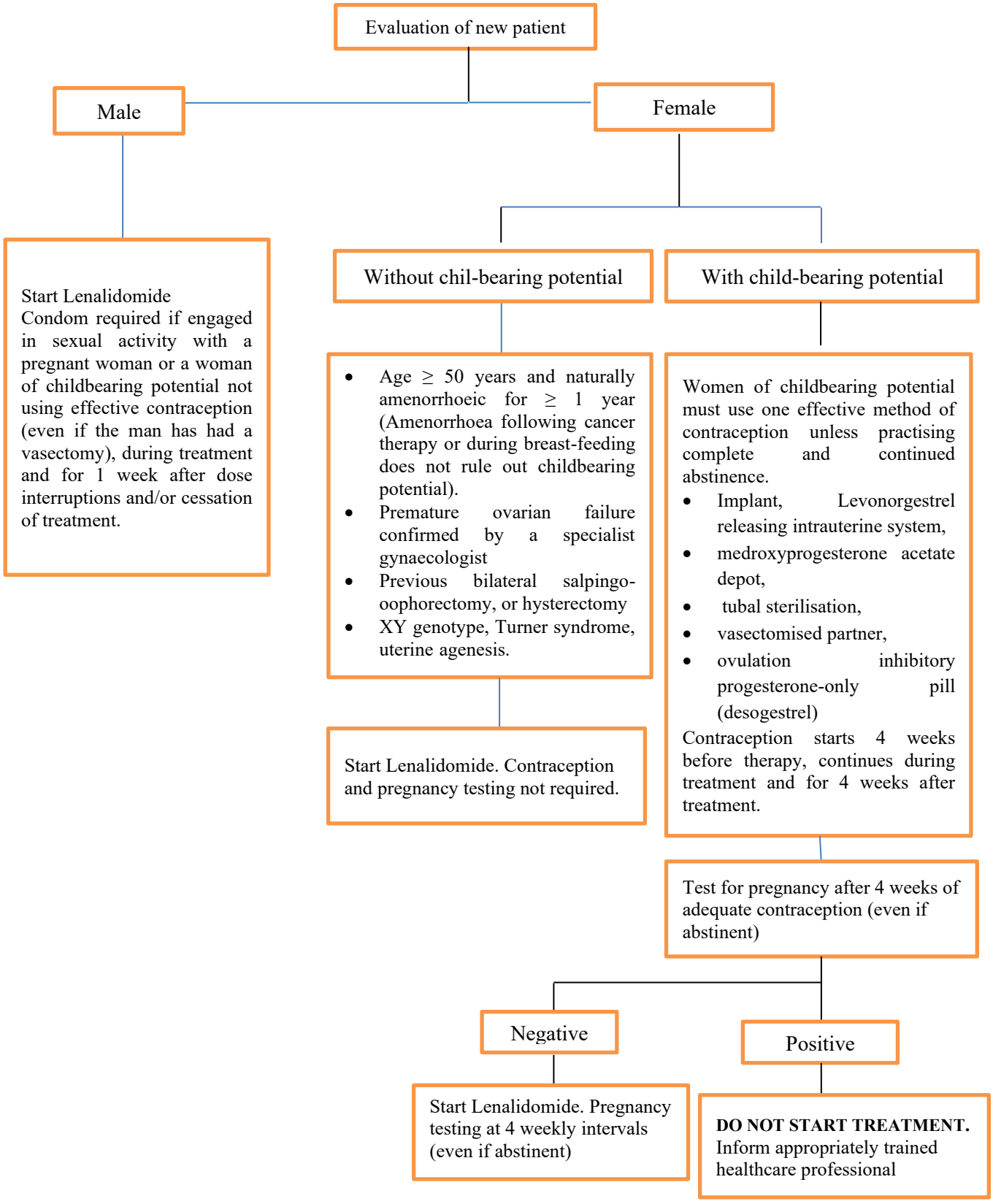
- All men and all women of childbearing potential should undergo, at treatment initiation, counselling regarding the need to avoid foetal exposure to lenalidomide during pregnancy.

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

- Patients must be provided with the appropriate Patient Guide and Risk Awareness Form.

- The physician will complete a Patient Card, which will be kept with the patient's medical records.

- The description of the Pregnancy Prevention Program and the categorisation of patients based on sex and childbearing potential is set out in the algorithm below:


Evaluation of new patient
Male
Female
Start Lenalidomide
Condom required 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), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
Without chil-bearing potential
With child-bearing potential
Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
Premature ovarian failure confirmed by a specialist gynaecologist
Previous bilateral salpingo-oophorectomy, or hysterectomy
XY genotype, Turner syndrome, uterine agenesis.
Start Lenalidomide. Contraception and pregnancy testing not required.
Women of childbearing potential must use one effective method of contraception unless practising complete and continued abstinence.
Implant, Levonorgestrel releasing intrauterine system,
medroxyprogesterone acetate depot,
tubal sterilisation,
vasectomised partner,
ovulation inhibitory progesterone-only pill (desogestrel)
Contraception starts 4 weeks before therapy, continues during treatment and for 4 weeks after treatment.
Test for pregnancy after 4 weeks of adequate contraception (even if abstinent)
Negative
Positive
Start Lenalidomide. Pregnancy testing at 4 weekly intervals (even if abstinent)
DO NOT START TREATMENT.
Inform appropriately trained healthcare professional

PRESCRIBING LENALIDOMIDE

Women of childbearing potential

- Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks according to the approved indications dosing regimens.
- Do not dispense to a woman of childbearing potential unless the pregnancy test is negative and has not been performed 3 days prior to the date of prescription.
- For women of childbearing potential, the medicine can be dispensed at a pharmacy no later than 7 days from the date of prescription.

All other patients

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

Female patient

Determine whether a female patient has a childbearing potential.

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- 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 breastfeeding does not rule out childbearing potential.

Healthcare professionals are advised to consult a gynecologist if there is any doubt whether woman meets the childbearing potential criteria.

DISPENSING LENALIDOMIDE

Pharmacy registration

It is a requirement of the Lenalidomide PPP that pharmacies wishing to purchase and dispense lenalidomide products are registered with these marketing authorisation holders. Registration involves reading and understanding the Healthcare Professional's Information Guide and completing a Pharmacy Registration form indicating agreement and compliance with the requirements of the lenalidomide pregnancy prevention program.

Dispensing of lenalidomide products will only be allowed from pharmacies registered with the Lenalidomide PPP. The relevant distributor will not authorise purchase and supply of these lenalidomide products to pharmacies not registered with the Lenalidomide PPP.

Lenalidomide is supplied to pharmacies registered with the Lenalidomide PPP only for the purpose of dispensing the product by the PPP registered pharmacy to the patient.

Ordering of lenalidomide:

The pharmacy must be registered with the Marketing Authorisation Holder of the lenalidomide product it wishes to dispense before it can order lenalidomide from that Marketing Authorisation Holder. To order a lenalidomide product the pharmacy must use a lenalidomide order form specific to the lenalidomide product it wishes to order.

PPP RECOMMENDATIONS FOR WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential must never take lenalidomide if they are:

- pregnant
- 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 must 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 finished, and even in case of dose interruption or
- commit to absolute and continuous abstinence on a monthly basis

AND

- have a medically supervised negative pregnancy test prior to issuing a prescription (with a minimum sensitivity of 25 mIU/ml) once she has been established on contraception for at least 4 weeks, at least in 4 weekly intervals 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 continued sexual abstinence.

- Patients should be advised to inform the healthcare professional 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 healthcare professional for contraceptive advice before initiating contraception.

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, 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. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and IUSs 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 is not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with severe neutropenia or severe thrombocytopenia.

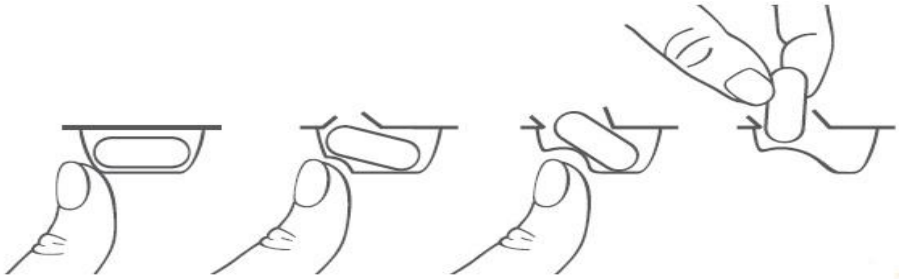
Your patient should be advised that if a pregnancy does occur whilst she is receiving lenalidomide, she must stop treatment immediately and immediately inform her prescriber.

PPP RECOMMENDATIONS 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 human semen during treatment. All male patients taking lenalidomide 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 and has no contraception.
- Patients should be instructed that if their partner does become pregnant whilst he is taking lenalidomidebor within 7 days after he has stopped taking lenalidomide he should inform his prescriber 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 at least 7 days following discontinuation of lenalidomide.

SAFETY ADVICE FOR HANDLING THE MEDICINAL PRODUCT: FOR HEALTHCARE PROFESSIONAS 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 as therefore the pressure is located to one site only which reduces the risk of capsule deformation or breakage (see below).



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. See below the proper technique for removing gloves.

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 the proper technique when removing gloves to prevent potential skin exposure (see over)
- Place gloves in a 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 this to Malta Medicines Authority via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

For further information regarding this medication please contact local representative: EJ Busuttil Ltd.
Phone: 2147184 (service is available 24/7)
Email: safety@ejbusuttil.com
Office Adress:
Busuttil Buildings, Triq l-Ghadam,
Central Business District Zone 1,
Birkirkara CBD1060 MALTA

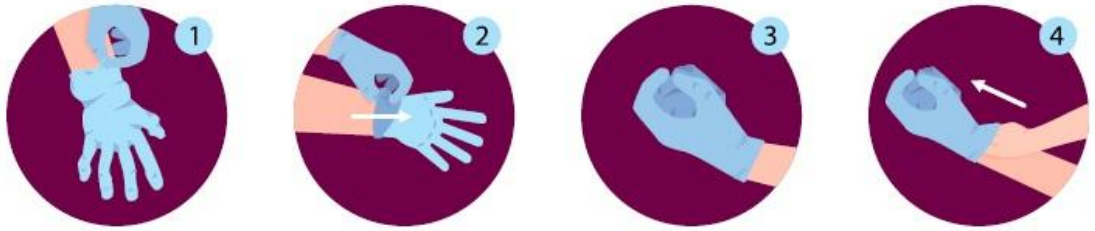
Adverse events should also be reported to AS GRINDEKS. Krustpils iela 53, Rīga, LV-1057, Latvia (Marketing Authorisation Holder) at: +371 67083644, E-mail: vigilance@grindeks

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 the powder gets in contact with your eye, 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.

DEMANDS IN CASE OF PREGNANCY

- Treatment must be stopped immediately if the patient is female.
- Patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.
- All such cases must be reported to Malta Medicines Authority via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

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- **Pregnancy Reporting Form** is included in this educational kit for the healthcare professional.
- AS Grindeks will contact you to monitor and control the fulfillment of this condition as well as monitor with you throughout pregnancy.

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

REPORTING ADVERSE EVENTS

The safe administration of lenalidomide is of paramount importance. As part of the ongoing safety monitoring the company wants to be informed about Adverse Reactions received during the administration of lenalidomide.
Adverse events should be reported to:

- Malta Medicines Authority via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

For further information regarding this medication please contact local representative: EJ Busuttil Ltd.
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CONTACT INFORMATION

For information and questions regarding the risk management associated with AS Grindeks medicine and the Pregnancy Prevention Program, please contact AS GRINDEKS: Krustpils iela 53, Rīga, LV-1057, Latvia (Marketing Authorisation Holder) at: +371 67083644, E-mail: vigilance@grindeks