Lenalidomide
Pregnancy Prevention Programme

Information for Healthcare Professionals

Prescribing or Dispensing Lenalidomide

UK

Risk Management contact details:
Tel: xxx
Fax: xxx
Email: xxx
Medical Information Queries: xxx

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This brochure contains the information needed for prescribing and dispensing lenalidomide, including information about the Pregnancy Prevention Programme (PPP). Please also refer to the Summary of Product Characteristics (SmPC) which can be found on the emc website: www.medicines.org.uk/emc for further information.

Lenalidomide Pregnancy Prevention Programme:

If lenalidomide is taken during pregnancy it is expected to cause severe birth defects or death to an unborn baby. This programme is designed to make sure that unborn babies are not exposed to lenalidomide. It will provide you with information about how to follow the programme and explain your responsibilities.

Other side effects of lenalidomide:

A full list of all side effects, further information and recommended precautions can be found in the lenalidomide SmPC.

Important information about the safe disposal of unwanted capsules and restrictions on donating blood during treatment is also included in this brochure.

This brochure will help you understand these problems and make sure you know what to do before prescribing and dispensing lenalidomide.

To ensure your patients' safety, please read this brochure carefully. You must ensure that your patients fully understand what you have told them about lenalidomide and that they have provided written confirmation on the Treatment Initiation Form, before starting treatment.

Contents

1.0 Introduction

Lenalidomide is an immunomodulating medicinal product.

Two Phase III clinical studies assessed lenalidomide maintenance in patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (ASCT) was assessed in (CALGB 100104 and IFM 2005 02).

In Study CALGB 100104, patients were randomised 1:1 within 90 to 100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on Days 1 to 28 of repeated 28-day cycles (increased up to 15 mg once daily after 3 months in the absence of dose limiting toxicity), and treatment was continued until disease progression.

The results of progression free survival (PFS) at unblinding (cut-off of 17 December 2009) showed a 62% reduction in risk of disease progression or death favouring lenalidomide over placebo. The Hazard Ratio was 0.38 (95% CI 0.27, 0.54; p <0.001). The median overall PFS was 33.9 months (95% CI not evaluable [NE], NE) in the lenalidomide arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm. The updated PFS, using a cut-off of 01 February 2016, continued to show a PFS advantage for lenalidomide (Hazard Ratio = 0.61; p <0.001).

In Study IFM 2005-02, patients who had undergone ASCT and had achieved at least a stable disease response at the time of haematologic recovery were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on Days 1 to 28 of repeated 28-day cycles increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity) following 2 courses of lenalidomide consolidation (25 mg/day, Days 1 to 21 of a 28-day cycle). Treatment was to be continued until disease progression. The study was unblinded upon the recommendationsof the data monitoring committee after surpassing the threshold for a preplanned interim analysis of PFS. After unblinding, patients receiving placebo were not crossed over to lenalidomide therapy prior to progressive disease. The lenalidomide arm was discontinued, as a proactive safety measure, after observing an imbalance of second primary malignancies (SPM). The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 07 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favouring lenalidomide over placebo. The Hazard Ratio was 0.52 (95% CI 0.41, 0.66; p <0.001). The median overall PFS was
40.1 months (95% CI 35.7, 42.4) in the lenalidomide arm versus 22.8 months (95% CI 20.7, 27.4) in the placebo arm. The updated PFS, using a cut-off of 01 February 2016 (96.7 months follow-up) continued to show a PFS advantage for lenalidomide (Hazard Ratio = 0.57; p <0.001).

A Phase III clinical study in newly diagnosed multiple myeloma (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e. until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). The study showed a statistically significant prolongation of PFS benefit in patients receiving Rd compared to MPT. The Hazard Ratio was 0.69 (p <0.001).

Another Phase III study in newly diagnosed multiple myeloma (MM-015) was conducted to evaluate the safety and efficacy of lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance therapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles.

The study showed a statistically significant prolongation of PFS benefit in patients receiving MPR+R compared to MPp+p (melphalan, prednisone, placebo + placebo maintenance). The Hazard Ratio was 0.37 (p <0.001).*

Information for healthcare professionals involved in the prescribing or dispensing of lenalidomide

In Phase III clinical studies in multiple myeloma with at least one prior therapy, the median time to progression (TTP) was 60.1 weeks in patients treated with lenalidomide/dexamethasone versus 20.1 weeks in patients treated with placebo/dexamethasone. The median PFS was 48.1 weeks in patients treated with lenalidomide/dexamethasone versus 20.0 weeks in patients treated with placebo/-dexamethasone.*

In a Phase III clinical study in myelodysplastic syndromes (MDS-004), a significant larger proportion of patients achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.*

In a phase II study of lenalidomide (N=170) versus single agent of investigator's choice of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine (N=84) in patients with mantle cell lymphoma (MCL) who were refractory to their last regimen or had relapsed one to three times (Study MCL-002), median PFS was significantly improved for lenalidomide versus investigator's choice (37.6 versus 22.7 weeks; Hazard Ratio = 0.61, p = 0.004).*

*text according to SmPC

1.1 Licensed Indication

Lenalidomide is an immunomodulating medicinal product.

- 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 as monotherapy is indicated for the treatment of adult 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.
  - All patients with myelodysplastic syndrome (MDS) should be informed that a prospective Post-Authorisation Safety Study to further evaluate the safety and monitor the usage of lenalidomide in this MDS patient population will be conducted in the UK.

AND

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

AND

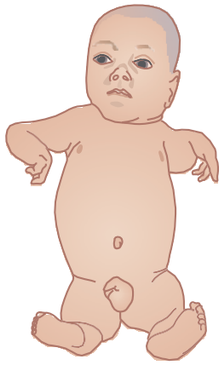
- Lenalidomide in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

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

1.2 Lenalidomide 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 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 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
- 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
- All men and all women of childbearing potential should undergo, at treatment initiation, counselling of the need to avoid pregnancy (this must be documented via a Treatment Initiation Form and checklists for counselling are provided with this pack)
- Patients should be capable of complying with the requirements of safe use of lenalidomide
- Patients must be provided with the appropriate Patient Brochure, Treatment Initiation Form and Patient Pocket Information Card.

All of the Lenalidomide Pregnancy Prevention Programme materials are contained within the Healthcare Professional's Information Pack and additional copies can be obtained by using the contact details displayed on the front of this brochure.

You must ensure that your patient fully understands what you have told them about lenalidomide before starting the treatment.

Information for healthcare professionals involved in the prescribing or dispensing of lenalidomide

In order to obtain lenalidomide, it is a requirement of the Pregnancy Prevention Programme that all healthcare professionals ensure that they have read and understood this pack before prescribing or dispensing lenalidomide for **any** patient.

- Prescribers must complete the appropriate Treatment Initiation Form with every patient before the first prescription is issued
- Pharmacies must register with Dr. Reddy's Laboratories to be able to order and dispense lenalidomide. To do this, the pharmacist must either; contact the Dr. Reddy's Laboratories Risk Management team using the details at the front of this brochure or use the paper Pharmacy Registration Form
- Every prescription for lenalidomide must be accompanied by a paper Prescription Authorisation Form, which is completed by the prescriber and the pharmacist
- The paper Pharmacy Registration Form and Prescription Authorisation Form are in subsequent sections of this pack.

All patients should be given a Patient Brochure and a Patient Pocket Information Card to take home – these materials remind patients of the key educational information and risks of treatment and can be found in the Information for Patients section.

For women of childbearing potential, prescriptions of lenalidomide should be limited to a maximum duration of 4 weeks according to the approved indications dosing regimens (posology) and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide should occur within a maximum of 7 days of the prescription, and the date of the last negative pregnancy test, must be within the 3 days prior to the date of the prescription.

For all other patients, prescriptions of lenalidomide should be limited to 12 weeks and continuation of treatment requires a new prescription. Pharmacists are required to send copies of every Prescription Authorisation Form immediately after dispensing to Dr. Reddy's Laboratories (Email: xxx or fax: xxx).

This Healthcare Professional's Information Pack also contains Adverse Event and Pregnancy Reporting Forms, Treatment Checklists, algorithms and Treatment Initiation Forms for obtaining consent.

In order to ensure that the actions to minimise the risk of foetal exposure are carried out for all patients, dispensing of lenalidomide will only be allowed from pharmacies registered with Dr. Reddy's Laboratories. Dr. Reddy's Laboratories will not authorise supply of lenalidomide to pharmacies that are not registered.

The following are core requirements of the Pregnancy Prevention Programme:

- All healthcare professionals dispensing or prescribing lenalidomide must read the Lenalidomide Healthcare Professional's Information Pack
- All pharmacies who dispense lenalidomide must agree to implement risk minimisation by registering with the Dr. Reddy's Laboratories Pregnancy Prevention Programme
- Every prescription for lenalidomide must be accompanied by a paper Prescription Authorisation Form, completed by the prescriber and the pharmacist, which a copy must be sent to Dr. Reddy's Laboratories.

1.3 Safety Advice Relevant to all Patients

In addition to information about the Pregnancy Prevention Programme, this brochure contains important advice for healthcare professionals about how to minimise the risk of adverse events during treatment with lenalidomide.

For further information about the appropriate use and safety profile of lenalidomide, please refer to the SmPC, which can be found on the emc website: www.medicines.org.uk/emc

You must send a copy of every completed Prescription Authorisation Form immediately to Dr. Reddy's Laboratories, for ALL patients, regardless of indication. This is an absolute requirement so that Dr. Reddy's Laboratories can fulfil regulatory obligations to monitor PPP adherence and off-label usage. Dr. Reddy's Laboratories is obliged to provide anonymous reports on this data to the regulatory agencies, to assess the effectiveness of risk minimisation activities and will not be able to comply if pharmacies do not provide ALL their Prescription Authorisation Forms to Dr. Reddy's Laboratories. Paper Prescription Authorisation Forms can be sent via email or fax, using the following contact details:

Tel: xxx
Fax: xxx
Email: xxx

If you wish to use email, please scan the completed form and email it as an attachment.

Please keep a copy of the Prescription Authorisation Forms for your records.

2.0 Therapeutic Management Advice to Avoid Foetal Exposure

2.1 Women of Non-childbearing Potential

Women in the following groups are considered **not** to have childbearing potential and do not need to undergo pregnancy testing or receive contraceptive advice:

- Age ≥ 50 years and naturally amenorrhoeaic for ≥ 1 year. Please note amenorrhoea following cancer therapy or during breastfeeding 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.

A female patient is considered to have childbearing potential unless she meets at least one of the above criteria. Prescribers are advised to refer their patient for a gynaecological opinion if at allunsure as to whether a woman meets the criteria for being of non-childbearing potential.

If a patient does not meet at least one of above criteria, but the prescriber considers the patient to be of non-childbearing potential, then prior approval of any deviation from these stipulated criteria should be sought from Dr. Reddy's Laboratories. This is a mandatory requirement. Please contact Dr. Reddy's Laboratories Risk Management(Tel: xxx Email: xxx). The following information is required to assess whether a patient, who does not meet at least one of the above criteria, can be treated as a women of non-childbearing potential:

- DOB and Initials of the Patient
- Details of why the prescriber considers the patient to be of non-childbearing potential
- Background to why a deviation has been requested.

2.2 Women of Childbearing Potential

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

- 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 25 mIU/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 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.

There must be no more than **3 days** between the dates of the last negative pregnancy test and the prescription. Best practice is for the pregnancy test, prescribing and dispensing to take place on the same day.

If not established on effective contraception, the patient must be referred to an appropriately trained healthcare 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).

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 ABSOLUTE AND CONTINUOUS ABSTINENCE AND PREGNANCY TEST IS NEGATIVE.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. If a patientis 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 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 immediately inform her prescriber.

Requirements in the event of a suspected pregnancy while on treatment with lenalidomide:

- **Stop treatment Immediately**
- **Refer the patient to a physician specialised or experienced in teratology for evaluation and advice.**
- **<u>Notify Dr. Reddy's Laboratories immediately</u> of all such occurrences by contacting Dr. Reddy's Laboratories Medical Information (Tel: xxx or email xxx). Please also complete the Pregnancy Reporting Form included in this pack. Dr. Reddy's Laboratories will wish to follow-up with you on the progress of allsuspected pregnancies in female patients or partners of male patient cases.**
- **Report the suspected pregnancy to the Medicine and Healthcare products Regulatory Agency (MHRA) via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.**

You can report the suspected pregnancy online via the Yellow Card website https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available:

- **by writing to FREEPOST YELLOW CARD (no other address details necessary);**
- **by emailing yellowcard@mhra.gov.uk;**
- **by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789;**
- **or by downloading and printing a form from the Yellow Card section of the MHRA website.**

2.3 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 does become pregnant whilst he is taking lenalidomide or 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.

If the partner of a male becomes pregnant, then he must inform his prescriber immediately, then:

Refer the female partner to a physician specialised or experienced in dealing with teratology for advice and evaluation.

Notify Dr. Reddy's Laboratories immediately by contacting Dr. Reddy's Laboratories Medical Information (Tel: xxx or email xxx). Please also complete the Pregnancy Reporting Form included in this pack. Dr. Reddy's Laboratories will wish to follow-up with you the progress of all suspected pregnancies in female patients or partners of male patient cases.

You can report the suspected pregnancy online via the Yellow Card website https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available:

- **by writing to FREEPOST YELLOW CARD (no other address details necessary);**
- **by emailing yellowcard@mhra.gov.uk;**
- **by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789;**
- **or by downloading and printing a form from the Yellow Card section of the MHRA website.**

2.4 Advice to all Patients

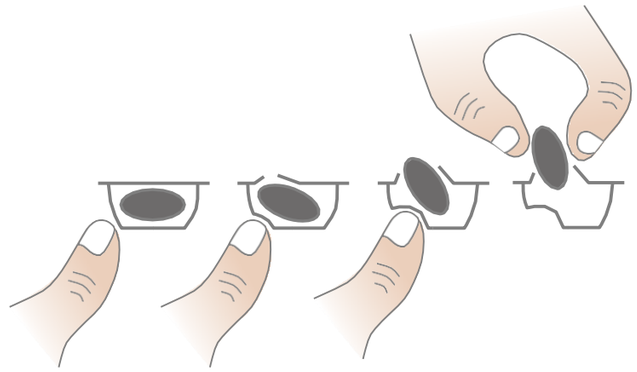
2.4.1 Points to Consider for Handling the Medicinal Product: For Healthcare Professionals and Caregivers

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

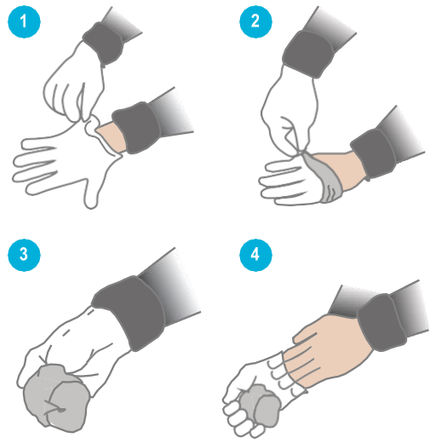
- If capsules are crushed or broken, dust containing drug substance may be released. Avoid dispersing the powder and avoid breathing the powder
- Wear disposable gloves to clean up the powder
- Place a damp cloth or towel over the powder area to minimise entry of powder into the air. Add excess liquid 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 Dr. Reddy's Laboratories Medical Information (Tel: xxx or email:xxx).

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.



Information for healthcare professionals involved in the prescribing or dispensing of lenalidomide

2.4.2 Blood Donation

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

2.5 Prescribing Lenalidomide

2.5.1 Maximum Prescription Lengths

Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks according to the approved indications dosing regimens (posology). 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. Lenalidomide treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of lenalidomide therapy and monitoring requirements.

2.5.2 Initial Prescription

Before issuing the initial prescription, you must:

- Counsel the patient on the safe use of lenalidomide in accordance with the measures described in this brochure and the SmPC, which can be found on the emc website: www.medicines.org.uk/emc
- Obtain their written confirmation (using the correct Treatment Initiation Form) that they have received and understood this information, and provide the patient with a copy
- Provide the patient with a Patient Brochure and a Patient Pocket Information Card
- A 'Prescription Authorisation Form' must be provided to the patient with each lenalidomide prescription and this will contain:
  - Patient initials, date of birth and diagnosis
  - Prescriber name, signature and date
  - Patient category (women of childbearing potential, women of non-childbearing potential or male)
  - Confirmation that they have received counselling about the teratogenic risk of lenalidomide and the required contraceptive measures for women of childbearing potential and male patients
  - For women of childbearing potential, the pregnancy test date and result
- That your patient is using effective contraception (if appropriate)

The patient must present their paper 'Prescription Authorisation Form' to the pharmacy along with their prescription and the pharmacy will check this form prior to dispensing lenalidomide.

2.5.3 Repeat of Subsequent Prescriptions

The patient must return to a prescriber for every repeat prescription of lenalidomide and a new Prescription Authorisation Form must be completed and submitted.

2.6 Dispensing Lenalidomide

It is a requirement of the Pregnancy Prevention Programme that pharmacies wishing to purchase and dispense lenalidomide are registered with Dr. Reddy's Laboratories. Registration involves receiving a Healthcare Professional's Information Pack and emailing, faxing or posting to Dr. Reddy's Laboratories a signed Pharmacy Registration Form to indicate agreement and compliance with the content.

Dispensing of lenalidomide will only be allowed from pharmacies registered with Dr. Reddy's Laboratories. Dr. Reddy's Laboratories will not authorise purchase and supply of lenalidomide to pharmacies not registered with Dr. Reddy's Laboratories.

Lenalidomide is supplied to pharmacies registered with Dr. Reddy's Laboratories' Risk Minimisation Program known as the UK Pregnancy Prevention Programme (PPP) only for the purpose of dispensing the product by the PPP registered pharmacy to the patient.

In order to be registered, the Chief Pharmacist or appointed deputy of the institution wishing to dispense must agree to implement the use of a Prescription Authorisation Form.

When completing the paper PAF, it asks the prescriber to confirm:

- The patient's diagnosis
- Whether the patient is male or female
- If female, the patient's childbearing potential
- If of childbearing potential that adequate contraception is in place and the date of the last negative pregnancy test, which must be within the **3 days** prior to the date of the prescription
- If male, counselling regarding the use of condoms has taken place
- That informed consent has been completed by the patient
- That the prescriber has read and understood the contents of this Healthcare Professional's Information Pack.

When completing the paper PAF, it asks the pharmacist to confirm:

- That the Prescription Authorisation Form has been completed in full by the prescriber
- That dispensing for women of childbearing potential is taking place within **7 days** of the prescription date
- That the pharmacist has read and understood the contents of this Healthcare Professional's Information Pack.

For women of childbearing potential, prescriptions for lenalidomide should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription and a new PAF completed and submitted. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide should occur within a maximum of 7 days of the prescription, and the date of the last negative pregnancy test, must be within the 3 days prior to the date of the prescription.

For males and women of non childbearing potential, prescriptions of lenalidomide should be limited to 12 weeks and continuation of treatment requires a new prescription and a new PAF completed and submitted.

Pharmacists are required to send a copy of **every** paper Prescription Authorisation Form to Dr. Reddy's Laboratories immediately after dispensing (email: xxx or Fax: xxx)

2.6.1 Dispensing Advice

- Please ensure that you dispense lenalidomide blisters intact; capsules must not be removed from blisters and packaged into bottles
- For each prescription, dispense a maximum of a 4 week supply for women of childbearing potential or a 12 week supply for all other patients
- Please educate all pharmacists within your pharmacy about the dispensing procedures for lenalidomide
- Instruct patients to return any unused lenalidomide to the pharmacy. Pharmacies must accept any unused lenalidomide returned by patients for destruction, and follow Good Pharmacy Practice guidelines for destruction of dangerous medicines.

3.0 Follow-up Assessment of the Effectiveness of the Programme

The terms of the Dr. Reddy's Laboratories Lenalidomide Marketing Authorisation require Dr. Reddy's Laboratories to assess the effectiveness of the Pregnancy Prevention Programme in order to ensure that all reasonable steps are being taken to reduce the risk of foetal exposure to lenalidomide.

Dr. Reddy's Laboratories is therefore obliged to perform audits at regular intervals and to report appropriately anonymous and aggregated results to the MHRA.

Dr. Reddy's Laboratories will conduct the audit from all of the completed Prescription Authorisation Forms received.

Pharmacies must complete and send a copy of every completed paper Prescription Authorisation Form immediately after dispensing to Dr. Reddy's Laboratories, then Dr. Reddy's Laboratories will be able to conduct the pharmacy audit using these forms. It is critical, therefore, that Prescription Authorisation Forms are completed accurately, and that pharmacies thereby assist Dr. Reddy's Laboratories to audit the effectiveness of the Pregnancy Prevention Programme.

Information for healthcare professionals involved in the prescribing or dispensing of lenalidomide

4.0 Posology

4.1 Newly Diagnosed Multiple Myeloma

4.1.1 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.

4.1.2 Lenalidomide in Combination with 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 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.

4.1.3 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/m^2 body surfacearea 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.

4.1.4 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 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.

4.2 Multiple Myeloma 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. Prescribers 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.

4.3 Myelodysplastic Syndromes

The recommended starting dose of lenalidomide is 10 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.

4.4 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.

4.5 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/m^2 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.

5.0 Selected 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).

5.1 Tumour Flare Reaction in Mantle Cell Lymphoma and Follicular Lymphoma Patients

Tumour flare reaction (TFR) has commonly been observed in patients with mantle cell lymphoma who were treated with lenalidomide and very commonly observed in patients 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 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.

5.2 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.

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

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 in risk of haematological SPM 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.

5.3 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. As a consequence, the benefit/risk balance of lenalidomide when MDS is associated with Del (5q) and complex cytogenetics is unknown (see Section 4.4 of the SmPC).

6.0 Reporting Adverse Events, Suspected and Confirmed Pregnancies, and Foetal Exposures

The safe use of lenalidomide is of paramount importance.

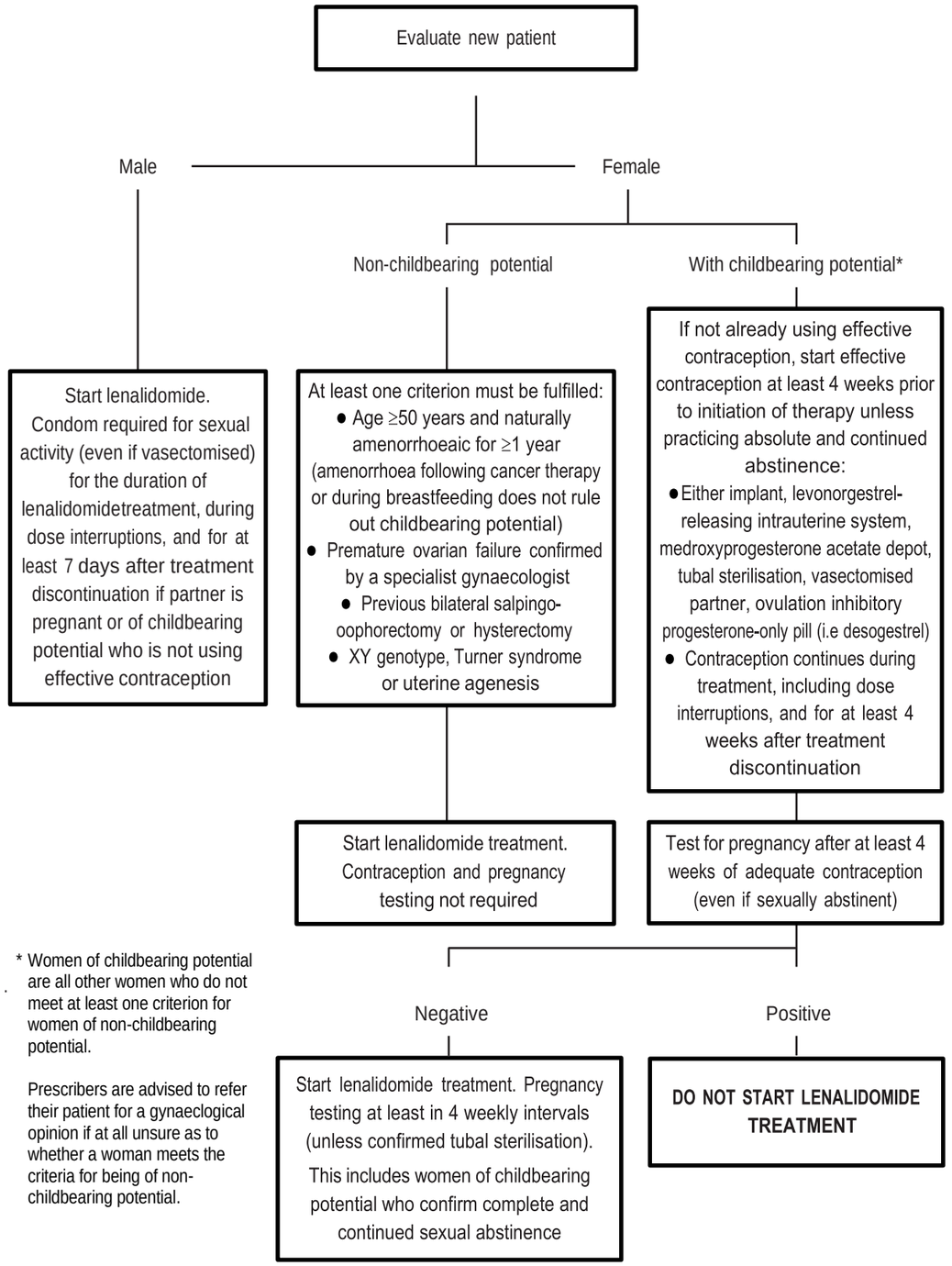
Adverse events (and cases of suspected or confirmed pregnancy or foetal exposure) should be reported. Adverse Event Report forms and Pregnancy Reporting forms are included in this pack and should be forwarded to Dr. Reddy's Laboratories Medical Information (Tel: xxx or email: xxx).

You can report the event online via the Yellow Card website https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary);
- by emailing yellowcard@mhra.gov.uk;
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789;
- or by downloading and printing a form from the Yellow Card section of the MHRA website.

Information for healthcare professionals involved in the prescribing or dispensing of lenalidomide

7.0 Description of the Pregnancy Prevention Programme and Patient Categorisation Algorithm



* Women of childbearing potential are all other women who do not meet at least one criterion for women of non-childbearing potential.

Prescribers are advised to refer their patient for a gynaeclogical opinion if at all unsure as to whether a woman meets the criteria for being of non-childbearing potential.

8.0 Contact Details

Risk Management:

For information and questions on the Risk Management of Dr. Reddy's Laboratories products, the Pregnancy Prevention Programme, pharmacy registrations and the use of the paper Prescription Authorisation Form.

Tel: xxx
Fax: xxx
Email: xxx

Medical Information:

To report any Adverse Events or suspected pregnancies to Dr. Reddy's Laboratories or obtain Medical Information on Dr. Reddy's Laboratories products.Tel: xxx
Email: xxx

Queries and Adverse Event reports can be reported at: xxx

Adverse events can also be reported online via the Yellow Card website https://yellowcard.mhra.gov.uk/ or searchfor MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary);
- by emailing yellowcard@mhra.gov.uk;
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789;
- or by downloading and printing a form from the Yellow Card section of the MHRA website.

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