Lenalidomide
Pregnancy Prevention Programme

Information for Healthcare Professionals Prescribing or Dispensing Lenalidomide

Important Safety Information:

Healthcare Professionals involved in the prescribing or dispensing of lenalidomide must read and understand the information contained within this brochure.For complete safety information please refer to the Summary of Product Characteristics (SmPC) for lenalidomide, available on the electronic medicines compendium (emc) website: www.medicines.org.uk/emc

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Pathfinder
Risk Management Platform

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

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 your Marketing Authorisation Holder's (MAH's) 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 guide carefully. You must ensure your patient's understanding about lenalidomide and that they have provided written confirmation on the Risk Awareness Form, before starting treatment.

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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 recommendations of 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).*

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

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

of treatment. Please refer to the SmPC for further information. This can be found on the UK electronic medicines compendium website: www.medicines.org.uk/emc/.

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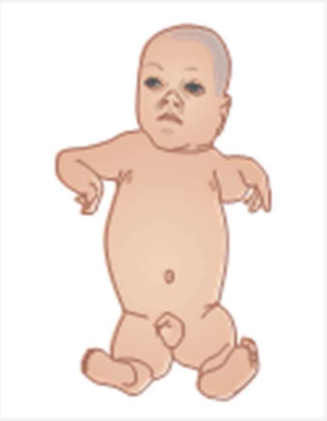
1.1 Lenalidomide Pregnancy Prevention Programme

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 in humans is expected. Lenalidomide is therefore contraindicated in pregnancy and in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme described in this HCP brochure 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 categorisation of patients based on sex and childbearing potential is set out in the algorithm available in this Healthcare Professional`s Information Guide, see section 6.0.
- All men and all women of childbearing potential should undergo, at treatment initiation, counselling regarding the need to avoid pregnancy (this must be documented via a Risk Awareness Form)
- Patients should be capable of complying with the requirements of safe use of lenalidomide.
- Patients must be provided with the appropriate Patient Brochure, Risk Awareness Form and Patient Pocket Information Card.

All lenalidomide Pregnancy Prevention Programme materials are contained within the Pathfinder PPP Platform as individual materials. Copies can be obtained by contacting the relevant MAH, using the contact details available within the Pathfinder PPP Platform or on the UK electronic medicines compendium website: www.medicines.org.uk/emc/.

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 the Additional Risk Minimisation Materials before prescribing or dispensing lenalidomide for **any** patient.

- Prescribers must register with lenalidomide Pregnancy Prevention Programme to be able to prescribe lenalidomide. To do this, the prescriber must visit https://pathfinderrmp.co.uk.
- Prescribers must complete the appropriate Risk Awareness Form for the patient before the first prescription is issued
- Pharmacists must register with lenalidomide Pregnancy Prevention Programme to be able to complete and approve Prescription Authorisation Forms (PAFs) and/or order and dispense lenalidomide. To do this, the pharmacist must visit https://pathfinderrmp.co.uk.
- Every prescription for Lenalidomide must be accompanied by a Prescription Authorisation Form (PAF), which can be completed electronically via the Pathfinder PPP platform by the prescriber and the pharmacist.
- Alternatively, only in case of a temporary system unavailability, an off-line version of the PAF will be made available, which upon completion must be sent immediately to PharmaCare Group Ltd (support@pharmacaregroup.co.uk).

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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 page of the Pathfinder platform.

For women of childbearing potential, prescriptions of lenalidomide should be limited to a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens 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 3 days prior to the date of the prescription.

For all other patients, prescriptions of lenalidomide can be for a maximum duration of treatment of 12 weeks and continuation of treatment requires a new prescription. Pharmacists are required to approve and mark every PAF as dispensed immediately upon dispensing either via the Pathfinder PPP platform or, in case of a temporary system unavailability, in an off-line PAF which shall be sent to PharmaCare Group Ltd. (support@pharmacaregroup.co.uk).

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 and pharmacists registered with the Pathfinder PPP. The Marketing Authorisation Holders will not authorise supply of their respective lenalidomide products to pharmacies that are not registered. For pharmacies utilising a third-party pharmacy to dispense the product to the patient, both the pharmacy completing and approving the PAF and the dispensing pharmacy are required to be registered with the lenalidomide Pregnancy Prevention Programme.

The following are core requirements of the lenalidomide Pregnancy Prevention Programme:

- All healthcare professionals dispensing or prescribing lenalidomide must read the Lenalidomide Pregnancy Prevention Programme materials.
- All pharmacists who dispense lenalidomide must agree to implement risk minimisation by registering with the Pathfinder Pregnancy Prevention Programme platform.
- If a registered third-party pharmacy is only dispensing lenalidomide, the pharmacy where the PAFs are being approved must also register with the Pathfinder Pregnancy Prevention Programme platform.
- Every prescription for lenalidomide must be accompanied by a PAF which can be completed electronically via the Pathfinder PPP platform by the prescriber and the pharmacist

1.2 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 UK electronic medicines compendium website: www.medicines.org.uk/emc/.

You must complete every PAF via the online Pathfinder PPP platform for ALL patients, regardless of indication or risk category. This is an absolute requirement so that the MAHs can fulfil their regulatory obligations to monitor PPP adherence and off-label usage.

Lenalidomide MAHs and PharmaCare Group Ltd are obliged to provide anonymised reports on this data to the MHRA, to assess the effectiveness of risk minimisation activities and will not be able to comply if pharmacists do not complete their PAFs or provide them to PharmaCare Group Ltd immediately.

2.0 Therapeutic Management Advice to Avoid Foetal Exposure

2.1 Women of Non-childbearing Potential (WNCBP)

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*.
- 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.

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 all unsure 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 Pharmacare Group (Tel: 0330 043 0908, Email: Support@pharmacaregroup.co.uk)..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 woman 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 (WCBP)

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 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, 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 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 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 the contraception about the lenalidomide treatment.

Patients should be advised to inform you if a change or stop of the 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 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).

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 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 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 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 female patient to a physician specialised or experienced in teratology for evaluation and advice.**
- **Immediately notify:**
    - **PharmaCare Group Ltd. on 0330 043 0908; email Support@pharmacaregroup.co.uk, and**
    - **the relevant MAH immediately, using:**
        - **the Pregnancy Reporting Form available within the Pathfinder PPP Platform, and**
- **the contact details available within the Pathfinder PPP Platform or on the UK electronic medicines compendium website: www.medicines.org.uk/emc/. You can report the suspected pregnancy via:**
- **the Yellow Card website www.mhra.gov.uk/yellowcard,**
- **theMHRA Yellow Card app, available in the Google Play or Apple App Store.**
- **some clinical IT systems (EMIS/SystemOne/Vision/MiDatabank) for healthcare professionals.**

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

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2.3 Men

In view of the expected teratogenic risk of lenalidomide, foetal exposure should be avoided.

Inform your patient about the effective contraceptive methods that his female partner can use.

Lenalidomide is present in human semen. As a precaution, all male patients taking lenalidomide, including those who have had a vasectomy as seminal fluid may still contain lenalidomide in the absence of spermatozoa, 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 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 patient taking lenalidomide 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.

- **Immediately notify:**
  - **PharmaCare Group Ltd. on 0330 043 0908; email Support@pharmacaregroup.co.uk, and**
  - **the relevant MAH immediately, using:**
    - **the Pregnancy Reporting Form available within the Pathfinder PPP Platform, and**
    - **the contact details available within the Pathfinder PPP Platform or on the Great Britain (GB) and Northern Ireland (NI) electronic medicines compendium websites: www.medicines.org.uk/emc (for Great Britain) or www.emcmedicines.com/en-GB/northernireland (for Northern Ireland).**
- **You can report the Suspected pregnancy via:**
  - **the Yellow Card website www.mhra.gov.uk/yellowcard**
  - **the MHRA Yellow Card app, available in the Google Play or Apple App Store or**
  - **some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals.**

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am to 5pm.

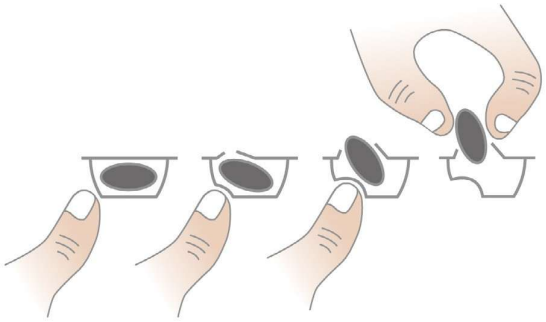
2.4 Advice to all Patients

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

Do not share the medicinal product with anyone else, even if they have similar symptoms. Store them safely so that no-one else can take them by accident and keep them out of the reach of children.

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. The pressure should be located at one site only, which reduces the risk of the capsule deforming or breaking (see figure below). Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Remove gloves carefully to prevent skin exposure. Place in a sealable plastic polyethylene bag. Dispose of any unused medication 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.
- Patients should be advised never to give the medicinal product to another person.

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

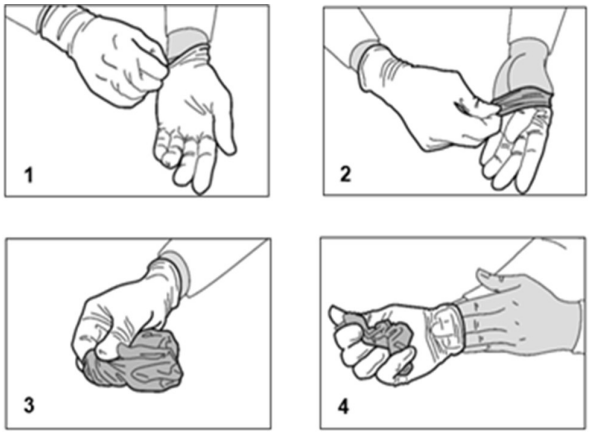
- If capsules are crushed or broken, dust containing drug substance may be released. Avoid dispersing the powder and avoid breathing on or inhaling the powder
- Wear disposable gloves to clean up the powder
- Place a damp cloth or towel over the powder area to minimise entry of powder into the air. Add 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. Dispose of it in accordance to local requirements for medicinal products
- Wash your hands thoroughly with soap and water after removing the gloves
- Please report to the relevant MAH immediately using the contact details available in the Pathfinder Pregnancy Prevention Programme (PPP) platform or on UK electronic medicines compendium website: www.medicines.org.uk/emc/.

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, being 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.



2.4.2 Blood Donation

Patients should not donate blood during treatment (including dose interruptions) 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 UK electronic medicines compendium website: www.medicines.org.uk/emc/.
- Obtain their written confirmation (using the correct Risk Awareness Form) that they have received and understood this information, and provide the patient with a copy
- Provide the patient with a Patient Brochure and Patient Pocked Information Card
- You must complete all necessary PAF fields in the Pathfinder PPP platform and provide the patient with only the prescription.
- In case of a temporary system unavailability, an off-line PAF must be completed with each lenalidomide prescription.
- Confirm that your patient is using an effective contraception (if applicable)

On completion of the PAF, the pharmacist will automatically receive it via the same system, will check this form and approve or reject, prior to dispensing lenalidomide.

In the event of a system outage, once the off-line PAF has been checked for completeness, a copy of the approved off-line PAF must be sent to PharmaCare Group Ltd. (support@pharmacaregroup.co.uk).

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2.5.3 Repeat of Subsequent Prescriptions

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

2.6 Dispensing Lenalidomide

It is a requirement of the Lenalidomide Pregnancy Prevention Programme that pharmacies and pharmacists wishing to order and dispense lenalidomide products are registered with the Pregnancy Prevention Programme platform. For pharmacies utilizing a third-party pharmacy to dispense the product to the patient, both the pharmacy completing and approving the PAF and the dispensing pharmacy are required to be registered with the lenalidomide Pregnancy Prevention Programme. After registration, each user will receive access to the Additional Risk Minimisation Materials via the Pathfinder PPP platform.

Dispensing of lenalidomide will only be allowed from pharmacies and by pharmacists registered with the Lenalidomide Pregnancy Prevention Programme. MAHs will not authorise purchase and supply of lenalidomide to pharmacies not registered with the Pathfinder platform.

In the event of a system outage, instruct the patient to provide the off-line PAF to their pharmacy. You must only dispense lenalidomide if the prescriber has annotated this form correctly.

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

- The patient's diagnosis
- The patient's risk category.
- 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 the patient's risk category is male, counselling regarding the use of condoms has taken place
- That the RAF has been completed by the patient.
- That the prescriber has read and understood the contents of the Healthcare Professionals' Information Guide.

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

- That the PAF has been completed in full by the prescriber
- That the supply dispensed is no more than a 4-week supply for a WCBP and no more than a 12-week supply for male and WNCBP patients
- 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 the Healthcare Professionals' Information Guide.

For women of childbearing potential, prescriptions for lenalidomide should be limited to 4 weeks of treatment 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.

Pharmacists are required to approve a PAF via the Pathfinder PPP platform for **every** dispensing or in case of a temporary system unavailability, complete and send an off-line PAF immediately after dispensing to PharmaCare Group Ltd (support@pharmacaregroup.co.uk).

Pharmacies should retain the original off-line PAF, if used in case of system unavailability, at the pharmacy premises for a minimum of 2 years.

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 maximum 12 week supply for all other patients.
- Instruct patients to return any unused lenalidomide capsules to the pharmacy. Pharmacies must accept any unused lenalidomide capsules 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 Lenalidomide Marketing Authorisation require every MAH 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.

PharmacareGroup Inc. as an administrator of the system is therefore monitoring the effectiveness of the programme at regular intervals and reports the results appropriately (anonymous and aggregated) to the MAHs and MHRA.

Pharmacare Group conducts the audit from all of the created PAFs.

Pharmacists must complete the lenalidomide PAF upon dispensing the product via the Pathfinder PPP platform. Pharmacare Group Ltd. will be able to review all PAFs. It is critical, therefore, that PAFs are completed accurately, and that physicians and pharmacists thereby assist Pharmacare Group Ltd.to audit the effectiveness of the Pregnancy Prevention Programme.

4.0 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).

4.1 Tumor 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 and very commonly observed in patients with follicular lymphoma treated with lenalidomide and rituximab. The patients at risk of TFR are those with high tumor burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation and appropriate precautions taken.

At the 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 nonsteroidal 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.

4.2 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 autologous stem-cell transplantation (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 tumor 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.

Please refer to the label for further details.

4.3 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).

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

The safe use of lenalidomide is of paramount importance.

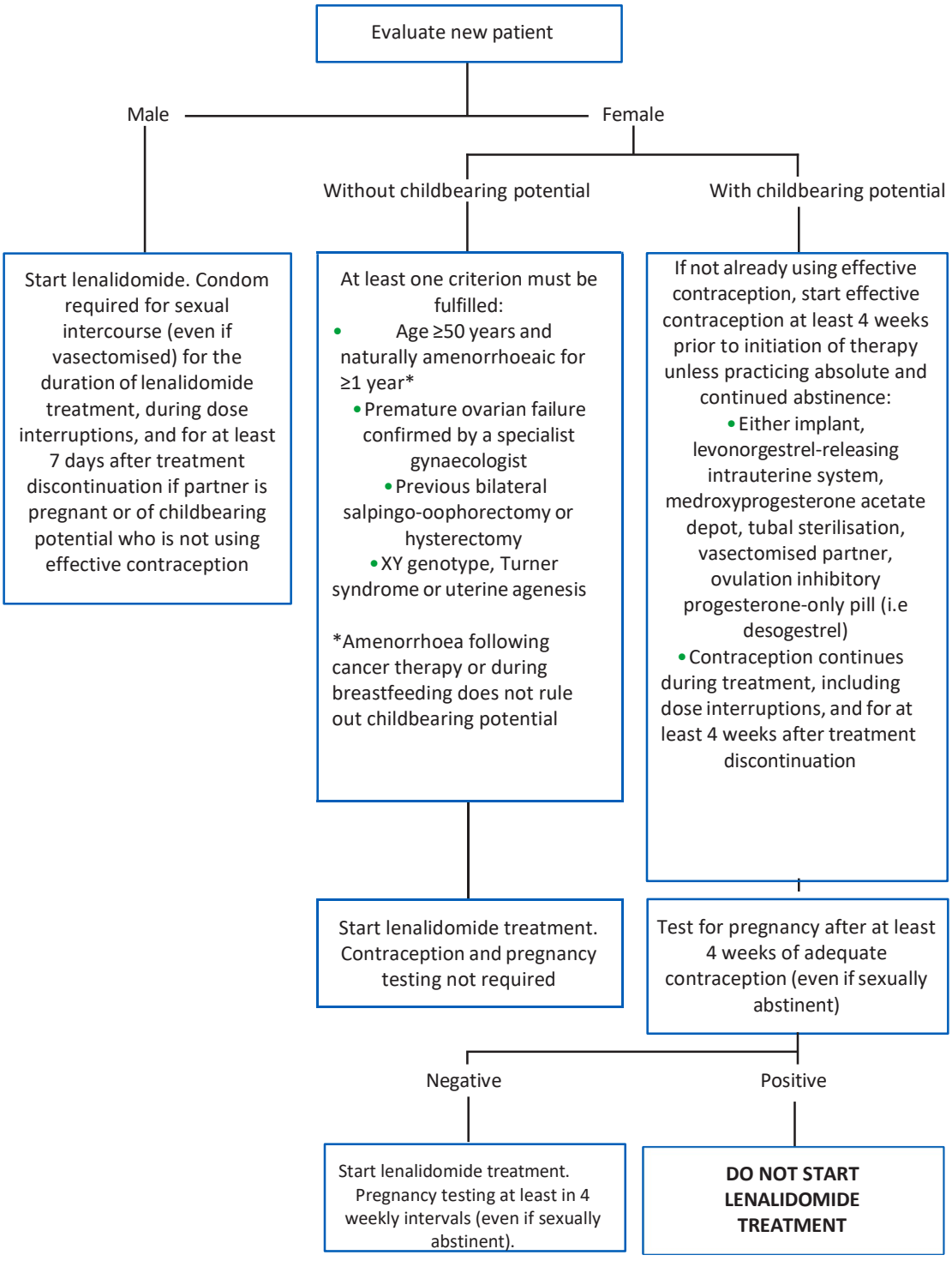
Adverse events (and cases of suspected or confirmed pregnancy or foetal exposure) should be reported. Adverse Event Report forms and Pregnancy Reporting forms are available in the Pathfinder Pregnancy Prevention Programme (PPP) platform and should be forwarded to the relevant MAH immediately using the contact details also available in the Pathfinder Pregnancy Prevention Programme (PPP) platform or on the UK electronic medicines compendium website: www.medicines.org.uk/emc/.

You can report the event or suspected pregnancy via:

- the Yellow Card Website www.mhra.gov.uk/yellowcard,
- the MHRA Yellow Card app, available in the Google Play or Apple App Store or

some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals.
Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

6.0 Patient Categorisation Algorithm



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7.0 Contact Details

Pathfinder PPP Platform technical Queries:

For technical information and questions on the Pathfinder please contact:

HealthBeacon

Email: clientsupport@healthbeacon.com

Tel: +44 203 936 8807

Mon - Fri 9am - 5pm GMT

Pathfinder PPP Platform Administrative Queries: For information and questions on the Risk Management of Lenalidomide, the Pregnancy Prevention Programme, please contact Pharmacare, please see contact details below.

Pharmacare Group

Email: support@pharmacaregroup.co.uk

Tel: 0330 043 0908

Mon - Fri 9am - 5pm GMT

Medical Information and Adverse Event

To report any Adverse Events or suspected pregnancies, or to obtain Medical Information on the respective medicinal product from the relevant Marketing Authorisation Holder, please find the contact details of each participating MAH in the Pathfinder PPP platform.

Data Protection Contact Details

Personal data is used solely for the purpose of entering you into the Pregnancy Prevention Programme and is processed by the relevant marketing authorisation holder, as marketing authorisation holder of pharmaceutical products and by the third-party service provider HealthBeacon and Pharmacare Group, to the extent and for as long as necessary, for the purposes of compliance with the Risk Management Plan legal obligations and for storage purposes. Should you have any queries in relation to the use of your personal data please contact support@pathfinderrmp.co.uk

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