PREGNANCY PREVENTION PROGRAM

LENALIDOMIDE SPC® *(lenalidomide)*

October, 2018
Ver. no. 0001

This document has been approved by the Saudi Food and Drug Authority (SFDA).

Introduction

LENALIDOMIDE SPC® (lenalidomide) is licensed for use in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy and Myelodysplastic syndromes (MDS) and Mantle cell lymphoma (MCL)

LENALIDOMIDE SPC® is a thalidomide analogue, a known human teratogenic substance that causes severe life-threatening birth defects. If LENALIDOMIDE SPC® is taken during pregnancy a teratogenic effect cannot be ruled out. LENALIDOMIDE SPC® is therefore contraindicated in pregnancy and in women of child-bearing potential unless the conditions of the Pregnancy Prevention Programme described in this pack are carried out.

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 SPC® for ANY patient.

For further information about the appropriate use and safety profile of LENALIDOMIDE SPC® please refer to the Summary of Product Characteristics (SPC) contained within this pack.

The pack also includes:

- Prescription authorisation forms (which must be completed for each prescription of LENALIDOMIDE SPC® – see later)
- A pharmacy authorisation agreement (all pharmacies dispensing LENALIDOMIDE SPC® must be registered with the Company so that distribution to that pharmacy can be authorised – see later)
- Checklists and algorithms to assist minimisation of the principle risks of treatment
- A patient information brochure and example informed consent form
- A pregnancy reporting form to assist urgent communication of information to the SUDAIR Pharma Company and the regulatory agencies of any instances of foetal exposure to LENALIDOMIDE SPC®
- An example letter containing important risk minimisation information to communicate to the GPs of patients taking LENALIDOMIDE SPC®
- Patient wallet cards carrying key information about the product and its safe use
- Adverse reaction report forms
- Further copies of this pack and the materials within it can be ordered from Sudair Pharma (contact details in Section 5) or by speaking to any Sudair Pharma representative.

The Pregnancy Prevention Programme (PPP)

The Pregnancy Prevention Programme (PPP) has the following mandatory elements:

- Patient and healthcare professional education
- Therapeutic management advice to avoid foetal exposure
- A distribution control system
- Follow-up assessment of the effectiveness of the Programme

A. Patient and healthcare professional education

All patients must sign an informed consent form confirming their awareness of the risks of treatment, particularly of the risks associated with foetal exposure and their agreement to adhere to the requirements of the programme.

All patients should be given a patient brochure to take home. The brochure has separate sections of information for women of child-bearing potential, women of non-childbearing potential and men.

All healthcare professionals involved in the prescribing or dispensing of lenalidomide must confirm that they have read this pack on the prescription authorisation form described below.

The Company is happy to provide further information and slide presentations on the PPP to any haematology department or pharmacy requesting it. Please contact the Medical Information and Drug Safety Department of Sudair Pharma.

B. Therapeutic management advice to avoid foetal exposure

Pregnancy testing

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

Prior to starting treatment

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

Follow-up and end of treatment

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

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Women of non-childbearing potential

Women in the following groups are considered NOT to have child-bearing potential and do not need to undergo pregnancy testing or receive contraceptive advice.

- Age ≥50 years and naturally amenorrhoeaic for ≥ U1 year. Please note amenorrhoea following cancer therapy does not rule out child-bearing potential

- Premature or during breast-feeding ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis

Treating physicians 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.

Women of child-bearing potential

In view of the potential teratogenic risk of LENALIDOMIDE SPC® foetal exposure must be avoided.

Women of child-bearing potential (even if they have amenorrhoea) must:

- Use two effective method of contraception for 4 weeks before therapy, during therapy, and until two reliable methods after LENALIDOMIDE SPC® therapy, and even in case of dose interruption
- You must not take LENALIDOMIDE SPC® if you are pregnant, as it is expected to be harmful to an unborn baby.
- You must not become pregnant while taking LENALIDOMIDE SPC®. There
- fore you must use effective methods of contraception if you are a woman of childbearing potential
- If you do become pregnant during your treatment with LENALIDOMIDE SPC®, you must stop the treatment and inform your doctor immediately.

or

- Commit to absolute and continuous abstinence

and

- Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25 IU/ml) once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy and 4 weeks after the end of therapy (unless confirmed tubal sterilization)

There must be no more than 3 days between the dates of the last negative pregnancy test and the last 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)
- Your patient should be advised that if a pregnancy does occur whilst she is receiving LENALIDOMIDE SPC®, she must stop treatment and inform her physician immediately.

Men

In view of the potential teratogenic risk of LENALIDOMIDE SPC®, foetal exposure should be avoided. It is not currently known if LENALIDOMIDE SPC® is present in semen therefore:

- Male patients should use condoms throughout the duration of treatment, during dose interruption and for one week after cessation of treatment if their wife is of child-bearing potential and has no contraception even if the male patient has undergone vasectomy.
- Male patients must not donate semen during therapy or for one week following the discontinuation of LENALIDOMIDE SPC®.
- Male patients should be instructed that if their partner becomes pregnant whilst taking LENALIDOMIDE SPC® or shortly after he has stopped he should inform his treating doctor immediately.

C. A distribution control system

In order to ensure that the actions to minimise the risk of foetal exposure are carried out for all patients, dispensing of LENALIDOMIDE SPC® will only be allowed from pharmacies registered with Sudair Pharma. The Company will not authorise supply of LENALIDOMIDE SPC® to pharmacies not registered with the Company.

In order to be registered the chief pharmacist or appointed deputy of the institution wishing to dispense must agree to implement and audit the use of a Prescription Authorisation Form (standard agreement letter and form enclosed with this pack).

The contents of the Prescription Authorisation Form can be incorporated into the institution's standard prescription or it can be used separately to the prescription but MUST accompany it.

The Prescription Authorisation Form asks the prescribing physician to confirm:

- Whether the patient is male or female
- If female, the patient's child-bearing potential
- If of child-bearing 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 that counselling regarding the use of condoms has taken place
- That informed consent has been completed by the patient
- That the physician has read and understands the contents of this pack
- The Prescription Authorisation Form asks the dispensing pharmacist to confirm:
- That the prescription and Prescription Authorization Forms have been completed in full
- That dispensing is taking place 7 DAYS OR LESS from the date of prescribing

- That the pharmacist has read and understood the contents of this pack

In addition to these measures the length of any prescription must be limited to one month though the prescription may be renewed up to 15 days prior to completion of the last cycle (i.e. not to be re-supplied within 13 days of any previous prescription).

D. Follow-up assessment of the effectiveness of the Programme

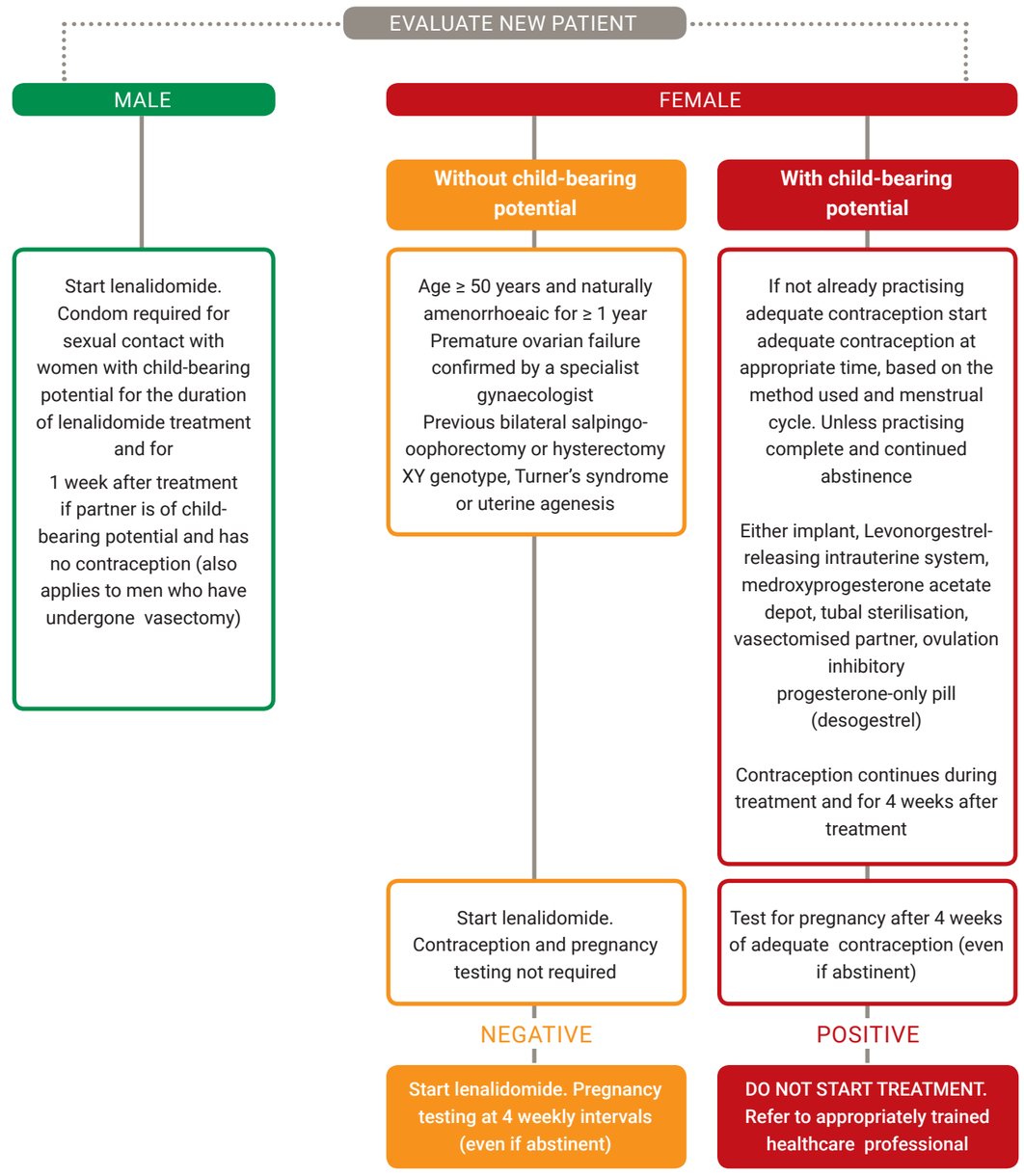
Sudair Pharma are committed to assessing and developing the effectiveness of this programme and will perform audits annually to gain feedback. The results of audit will be discussed with SFDA .

Pharmacy registration with the Company to dispense LENALIDOMIDE SPC® requires that pharmacies perform an annual internal audit of the process. The Company will supply an audit tool to assist this and is required by Saudi Food and Drug Authority (SFDA) to report the collated results of such an audit.

In the event of pregnancy whilst on treatment with LENALIDOMIDE SPC®

- Stop treatment
- Refer patient to a physician specialised or experienced in teratology for evaluation and advice Notify Sudair Pharma immediately by contacting the Sudair Pharma Drug Safety Department (contact details in section 5) and completing the Pregnancy Capture Form included in this pack. Sudair Pharma will wish to follow-up with you the progress of all pregnancies
- Report the event to the SFDA using the following contact:
  - National Pharmacovigilance and Drug Safety Center
  - E-mail: npc.drug@sfda.gov.sa
  - Online: https://ade.sfda.gov.sa
  - Toll free phone: 8002490000
  - Fax: +966112057662

Algorithm For Implementation Of PPP



Warnings And Precautions

Programme in female patients

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless it has been proven that the patient cannot become pregnant.

Criteria for clarification of the potential for pregnancy.

A female patient or the female partner of a male patient is classified as having childbearing potential unless she fulfils at least one of the following conditions:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 years *
- Premature ovarian failure confirmed by a gynaecologist
- Female that has not begun menstruation
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner's syndrome, uterine agenesis

**** Amenorrhoea following cancer therapy does not rule out childbearing potential***

Reporting Of Adverse Reactions

The safe use of LENALIDOMIDE SPC® is of paramount importance. As part of the ongoing safety monitoring Sudair Pharma wishes to learn of Adverse Reactions that have occurred during the use of LENALIDOMIDE SPC®.

Adverse Reaction report forms are included in this Healthcare Professional Pack and should be forwarded to the Sudair Pharma Drug Safety Department at the address below. They should also be reported to the SFDA using the following:

National Pharmacovigilance and Drug Safety Center:

E-mail:	**npc.drug@sfda.gov.sa**
Online:	**https://ade.sfda.gov.sa**
Toll free phone:	**800 249 0000**
Fax:	**+966 11 205 7662**

Sudair Pharma Drug Safety And Medical Information Contact Details

Tell:	**+966 11 466 8193**
Fax:	**+966 11 466 8195**
Mailing:	**P.O. Box 19047 Riyadh, Saudi Arabia**
Email:	**S.AlThobaiti@SudairPharma.com**

Sudair Pharma King Fahd road, Building 911 Riyadh, Saudi Arabia

Or

E-mail:	**npc.drug@sfda.gov.sa**
Online:	**https://ade.sfda.gov.sa**
Toll free phone:	**8002490000**
Fax:	**+966112057662.**

LENALIDOMIDE SPC® Risk Evaluation And Mitigation Strategy (REMS)

Program Education And Prescribing Safety

PROGRAM EDUCATION AND PRESCRIBING SAFETY

Authorization No.:

Confirmation No.:

Confirmation Date:

Pharmacy Name:

Pharmacy Address:

Counselor Name:

Work Phone:

Ext.:

Patient Name:

Date of Birth:

Risk Category:

Checklist for female patients of reproductive potential

I will make sure that patients are aware that they will receive the Medication Guide along with their prescription	

I COUNSELED ADULTS AND CHILDREN ON

Potential embryo-fetal toxicity	
Not taking LENALIDOMIDE SPC® (lenalidomide) if pregnant or breastfeeding	
Using at the same time at least 1 highly effective method—tubal ligation, IUD, hormonal (birth control pills, hormonal patches, injections, vaginal rings, or implants), or partner's vasectomy—and at least 1 additional effective method of birth control—male latex or synthetic condom, diaphragm, or cervical cap—every time they have sex with a male, or abstaining from sex with a male	
Unacceptable methods of birth control are progesterone-only "mini-pills," IUD Progesterone T, female condoms, natural family planning (rhythm method) or breastfeeding, fertility awareness, withdrawal, and cervical shield (a cervical shield should not be confused with a cervical cap, which is an effective secondary form of contraception)	

Continuing to use at the same time at least 1 highly effective method and at least 1 additional effective method of birth control beginning at least 4 weeks before taking LENALIDOMIDE SPC®, while taking LENALIDOMIDE SPC®, during dose interruptions, and for at least 4 weeks after stopping LENALIDOMIDE SPC® every time they have sex with a male, or abstaining from sex with a male	
Obtaining a pregnancy test—performed by their healthcare provider—weekly during the first 4 weeks of use. Thereafter, pregnancy testing should be repeated every 4 weeks during the rest of their treatment in females with regular menstrual cycles or no cycle at all. If menstrual cycles are irregular, the pregnancy testing should occur every 2-weeks	
The need to stop taking LENALIDOMIDE SPC® right away in the event of becoming pregnant, or if they think for any reason they may be pregnant, and to call their healthcare provider immediately	
Possible side effects include neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism as well as risk of myocardial infarction and stroke	
The need for del 5q MDS patients to schedule a blood test every week for the first 8 weeks and monthly thereafter to monitor blood counts while taking LENALIDOMIDE SPC®	
Not sharing LENALIDOMIDE SPC® capsules with anyone—especially with females who can get pregnant	
Not donating blood while taking LENALIDOMIDE SPC® (including dose interruptions) and for 4 weeks after stopping LENALIDOMIDE SPC®	
Not breaking, chewing, or opening LENALIDOMIDE SPC® capsules	
Instructions on LENALIDOMIDE SPC® dose and administration	
Milligram (mg) Strength:	**Number of Capsules Dispensed:**

Checklist for female patients not of reproductive potential (natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy)

I will make sure that patients are aware that they will receive the Medication Guide along with their prescription	

I COUNSELED ADULTS AND CHILDREN ON

Possible side effects include neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism as well as risk of myocardial infarction and stroke	
The need for del 5q MDS patients to schedule a blood test every week for the first 8 weeks and monthly thereafter to monitor blood counts while taking LENALIDOMIDE SPC®	
Not sharing LENALIDOMIDE SPC® capsules with anyone—especially with females who can get pregnant	
Not donating blood while taking LENALIDOMIDE SPC® (including dose interruptions) and for 4 weeks after stopping LENALIDOMIDE SPC®	
Not breaking, chewing, or opening LENALIDOMIDE SPC® capsules	
Instructions on LENALIDOMIDE SPC® dose and administration	
Milligram (mg) Strength:	**Number of Capsules Dispensed:**

Checklist for male patients

I will make sure that patients are aware that they will receive the Medication Guide along with their prescription	

I COUNSELED ADULTS AND CHILDREN ON

Potential embryo-fetal toxicity and contraception (wearing a latex or synthetic condom every time when engaging in sexual intercourse with a female who can get pregnant, even if the patient has had a successful vasectomy)	
Female partners of males taking LENALIDOMIDE SPC® (lenalidomide) must call their healthcare provider right away if they get pregnant	
Possible side effects include neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism as well as risk of myocardial infarction and stroke	
The need for del 5q MDS patients to schedule a blood test every week for the first 8 weeks and monthly thereafter to monitor blood counts while taking LENALIDOMIDE SPC®	
Not sharing LENALIDOMIDE SPC® capsules with anyone—especially with females who can get pregnant	
Not donating blood or sperm while taking LENALIDOMIDE SPC® (including dose interruptions) and for 4 weeks after stopping LENALIDOMIDE SPC®	
Not breaking, chewing, or opening LENALIDOMIDE SPC® capsules	
Instructions on LENALIDOMIDE SPC® dose and administration	
Milligram (mg) Strength:	**Number of Capsules Dispensed:**

MALE CHILDREN (<18 YEARS OF AGE)

Parent or legal guardian must have read the LENALIDOMIDE SPC® education material and agreed to ensure compliance	

All boxes and spaces must be marked or filled in during counseling with the patient for every prescription.

Counselor Signature: **Date:**

Tell: **+966 11 466 8193**

Sudair Pharma, King Fahad road, Building 911 Riyadh, Saudi Arabia

Mailing: **P.O. Box 19047 Riyadh, Saudi Arabia**

National Pharmacovigilance and Drug Safety Center:

E-mail: **npc.drug@sfda.gov.sa**

Online: **https://ade.sfda.gov.sa**

Toll free phone: **8002490000**

Fax: **+966 11 205 7662**

Please see full Prescribing Information, including Boxed Warnings, Contraindications, Warnings And Precautions, and Adverse Reactions, enclosed

Treatment Initiation Form

Treatment Initiation Form

Warning: Severe life-threatening birth defects. If LENALIDOMIDE SPC® is taken during pregnancy it can cause severe birth defects or death to an unborn baby.

Patient Details

Patient First Name:			
Patient Last Name:			
Date of Birth:		**Counselling Date:**	

Pregnancy Prevention Referral

Pregnancy prevention referral required				Y or N
Pregnancy prevention referral made		DD	MM	YYYY
Pregnancy prevention consultation conducted on		DD	MM	YYYY

Pregnancy Prevention

The patient has been established on one of the following for at least 4 weeks	Tick
Implant Tick	Tick
Levonorgestrel-releasing intrauterine system (IUS)	Tick
Medroxyprogesterone acetate depot	Tick
Tubal sterilization	Tick
Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses	Tick
Ovulation inhibitory progesterone-only pills (i.e. desogestrel)	Tick
Committed to complete and absolute abstinence	Tick

Pregnancy Test

Pregnancy test date:	DD	MM	YYYY	**Result:**	Positive/Negative

LENALIDOMIDE SPC® treatment cannot start until the patient has been established on effective method of pregnancy prevention for 4 weeks, or commits to complete and continuous abstinence, and obtains a negative pregnancy test

Prescriber Confirmation

I have fully explained to the patient named above the nature, purpose and risks of the treatment associated with LENALIDOMIDE SPC® especially the risks to women of childbearing potential.

Prescriber First Name :					
Prescriber Last Name:					
Prescriber Signature:		**Date:**	DD	MM	YYYY

Patient: please read thoroughly and initial the adjacent box if you agree with the statement

I understand that severe birth defects can occur with the use of thalidomide. I have been warned by my doctor that any unborn baby has a high risk of birth defects and could even die if a woman is pregnant or becomes pregnant while taking LENALIDOMIDE SPC®	Patient initials
I understand that I must not take lenalidomide if I am pregnant or plan to become pregnant.	Patient initials
I understand that I must use 2 effective method of pregnancy prevention without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment.	Patient initials
I understand that if I need to change or stop my method of pregnancy prevention I will discuss this first with the physician prescribing my pregnancy prevention method the physician prescribing my LENALIDOMIDE SPC®	Patient initials
I understand that before starting LENALIDOMIDE SPC® treatment I must have a pregnancy test.	Patient initials
I will then have a pregnancy test every 4 weeks during treatment, and a final test 4 week after the end of treatment	Patient initials
I understand that I must immediately stop taking LENALIDOMIDE SPC® and inform my doctor if I become pregnant while taking this drug; or if I miss my menstrual period or experience any unusual menstrual bleeding; or think FOR ANY REASON that I may be pregnant	Patient initials
I understand that LENALIDOMIDE SPC® will be prescribed ONLY for me. I must not share it with ANYONE	Patient initials
I have read the LENALIDOMIDE SPC® patient booklet and understand the contents, including the information about other possible health problems (side effects) from LENALIDOMIDE SPC®	Patient initials
I know that I cannot donate blood while taking LENALIDOMIDE SPC®, or for 1 week after stopping treatment	Patient initials
I understand that I must return any unused LENALIDOMIDE SPC® to my pharmacy at the end of my treatment	Patient initials
I understand that I must provide a copy of this form to my pharmacy prior to obtaining my first prescription	Patient initials

Patient Confirmation

I confirm that I understand and will comply with the requirements of the LENALIDOMIDE SPC® Pregnancy Prevention Programme, and I agree that my doctor can initiate my treatment with LENALIDOMIDE SPC®.

Prescriber Signature:		**Date:**	DD	MM	YYYY

This form based on the brand

يرجى قراءة المربع المجاور بالكامل ووضع علامة ✓ إذا كنت توافق

اتفهم أن هناك عيوب خلقية شديدة يمكن أن تحدث للجنين عند استخدام اللينالیدوميد خلال فتره الحمل وقد تم تحذيري من قبل الطبيب الخاص بي بأن أي طفل لم يولد بعد فهو عرضة لمخاطر كبيرة من العيوب والتشوهات الخلقية ويمكن ايضاً أن يموت الجنين إذا كانت المرأة حامل أو اصبحت حاملاً أثناء تناول لينالیدوميد اس بي سي	
أتفهم أنني يجب أن لا أتناول اللينالیدوميد إذا كنت حامل أو أخطط للحمل.	
اتفهم أنه لا بد لي من استخدام طريقتين فعالة للوقاية من الحمل دون انقطاع , ٤ أسابيع قبل بدء العلاج، طوال مدة العلاج، و ٤ أسابيع بعد نهاية العلاج.	
أتفهم أنني إذا كنت بحاجة إلى تغيير أو إيقاف طرق منع الحمل ، فسيتم اولاً مناقشتها مع : • الطبيب الذي وصف لي طريقة الوقاية من الحمل • الطبيب الذي وصف لينالیدوميد اس بي سي	
اتفهم أنه قبل البدء في استخدام علاج لينالیدوميد اس بي سي يجب أن أجري اختباراً للحمل.	
سوف أجري اختبار الحمل كل ٤ أسابيع أثناء فترة العلاج ، واختبار نهائي بعد ٤ أسابيع من نهاية استخدام العلاج	
اتفهم أنه يجب علي التوقف عن تناول لينالیدوميد فوراً وإبلاغ طبيبي إذا حصل حمل أثناء تناول الدواء , أو إذا تأخر أو عدم إنتظام في فترة الحيض فترة الحيض أو تعرضت لنزيف غير طبيعي , أو الاعتقاد لأي سبب من الأسباب أنني قد اكون حاملا .	
اتفهم أن لينالیدوميد اس بي سي سوف يتم وصفه لي فقط وعليه يجب أن لا أشاركه مع أي شخص اخر.	
لقد قرأت النشرة الداخلية للمريض الخاصة بمستحضر لينالیدوميد اس بي سي وفهمت محتوياتها ، بما في ذلك المعلومات حول المشاكل الصحية المحتملة الأخرى (الآثار الجانبية)	
أعلم أنه لا يمكنني التبرع بالدم أثناء تناول اللينالیدوميد اس بي سي ، كذلك لمدة ٤ أسابيع من بعد التوقف عن استخدام العلاج	
اتفهم انه عند الانتهاء من العلاج يجب عليّ أن أعيد أي كمية من اللينالیدوميد اس بي سي الغير مستخدمة إلى صيدلية المستشفى التي تم صرف الوصفه منها.	
أتفهم أنه يجب عليّ تقديم نسخة من هذا النموذج إلى الصيدلية قبل الحصول على أول وصفة	

اقرار المريض

انا أقر أنهٌ يمكن لطبيبي البدأ بإستخدام اللينالیدوميد اس بي سي لعلاجي ، و أؤكد أني اتفهم و موافق على متطلبات برنامج اللينالیدوميد اس بي سي

توقيع المريض		**التاريخ**	اليوم	الشهر	السنة

LENALIDOMIDE SPC® (Lenalidomide) Dispense Authorisation Form (DAF)

Name of treating hospital	
Patient date of birth	Patient Initials (first, middle, last)
Prescribing physician (print)	
Diagnosis	
Is this patient being treated in accordance with NICE guidance for LENALIDOMIDE SPC®? Y or N	
Is this patient being treated outside of the final NICE guidance for LENALIDOMIDE SPC®, but eligible for the LENALIDOMIDE SPC® Options Scheme? - Y or N	
Capsule strength prescribed:	5 mg / 10 mg / 25 mg
Please enter the cycle number of LENALIDOMIDE SPC® prescribed for this patient	

Please tick all boxes that apply

Woman of non-childbearing potential	
Male	
The patient has been counselled about the teratogenic risk of treatment with LENALIDOMIDE SPC® and understands the need to use a condom if involved in sexual activity with a woman of childbearing potential (even if the patient has had a vasectomy).	

Note to pharmacist – do not dispense unless ticked

Woman of childbearing potential	
The patient has been counselled about the teratogenic risk of treatment and the need to avoid pregnancy, and has been on effective contraception for at least 4 weeks?	
Date of last negative pregnancy test	

Note to pharmacist – do not dispense unless ticked and a negative test has been conducted within 3 days prior of the prescription date

Both signatures must be present prior to dispensing LENALIDOMIDE SPC®

Dispenser's declaration

I am a physician experienced in managing haematological malignancy and I have read and understood the LENALIDOMIDE SPC® Healthcare Professional's Information Pack and confirm that the patient has signed an informed consent for LENALIDOMIDE SPC treatment.

Sign	Date
	Bleep
Print	

Note to pharmacist – prescription and Prescription Authorisation Form must have the same date

Pharmacist's declaration

I am satisfied that this LENALIDOMIDE SPC® Prescription Authorisation Form has been completed fully, confirm that dispensing is taking place within 7 days of the date of prescription and that I have read and understood the LENALIDOMIDE SPC® Healthcare Professional's Information Pack.

Sign	Date
	Bleep
Print	
Name and postcode of dispensing pharmacy	

Date faxed to SPC	Faxed by (Name)

This form based on the brand

LENALIDOMIDE SPC® (Lenalidomide) Dispense Authorisation Form (DAF)

LENALIDOMIDE SPC® (Lenalidomide) Prescription Authorisation Form (PAF)

Name of treating hospital	
Patient date of birth	Patient Initials (first, middle, last)
Prescribing physician (print)	
Diagnosis	
Is this patient being treated in accordance with NICE guidance for LENALIDOMIDE SPC®? Y or N	
Is this patient being treated outside of the final NICE guidance for LENALIDOMIDE SPC®, but eligible for the LENALIDOMIDE SPC® Options Scheme? - Y or N	
Capsule strength prescribed:	5 mg ☐ 10 mg ☐ 25 mg ☐
Please enter the cycle number of LENALIDOMIDE SPC® prescribed for this patient	

Please tick all boxes that apply

Woman of non-childbearing potential	☐
Male	☐
The patient has been counselled about the teratogenic risk of treatment with LENALIDOMIDE SPC® and understands the need to use a condom if involved in sexual activity with a woman of childbearing potential (even if the patient has had a vasectomy).	☐

Note to pharmacist – do not dispense unless ticked

Woman of childbearing potential	☐
The patient has been counselled about the teratogenic risk of treatment and the need to avoid pregnancy, and has been on effective contraception for at least 4 weeks?	☐
Date of last negative pregnancy test	

Note to pharmacist – do not dispense unless ticked and a negative test has been conducted within 3 days prior of the prescription date

Both signatures must be present prior to dispensing LENALIDOMIDE SPC®

Prescriber's declaration (Consultants only)

I am a physician experienced in managing haematological malignancy and I have read and understood the LENALIDOMIDE SPC® Healthcare Professional's Information Pack and confirm that the patient has signed an informed consent for LENALIDOMIDE SPC treatment.

Sign	Date
	Bleep
Print	

Note to pharmacist – prescription and Prescription Authorisation Form must have the same date

Pharmacist's declaration

I am satisfied that this LENALIDOMIDE SPC® Prescription Authorisation Form has been completed fully, confirm that dispensing is taking place within 7 days of the date of prescription and that I have read and understood the LENALIDOMIDE SPC® Healthcare Professional's Information Pack.

Sign	Date
	Bleep
Print	
Name and postcode of dispensing pharmacy	

Date faxed to SPC	Faxed by (Name)

This form based on the brand

LENALIDOMIDE SPC® (Lenalidomide) Prescription Authorisation Form (PAF)

Pregnancy Reporting Form

Pregnancy Reporting Form

Please complete this form to report a pregnancy in a patient (or in a female partner of a male patient) treated with LENALIDOMIDE SPC®.

As part of Sudair Pharma Safety Monitoring System, it is essential that we follow-up on all reported pregnancies.

Sudair Pharma will therefore be in contact with you for further information in due course and would value your co- operation to ensure we are able to obtain all relevant information regarding foetal exposure to our products.

Please fax or email immediately to Sudair Pharma Drug Safety at the number/address below:

Tell: **+966 11 466 8 193**

Fax: **+966 11 466 8 195**

Sudair Pharma King Fahd road, Building 911 Riyadh, Saudi Arabia

Mailing: **P.O. Box 19047 Riyadh, Saudi Arabia**

Email: **S.AlThobaiti@SudairPharma.com**

Or

E-mail: **npc.drug@sfda.gov.sa**

Online: **https://ade.sfda.gov.sa**

Toll free phone: **800 249 0000**

Fax: **+966 11 205 7662**

Reporter's Details

Title: Mr, Mrs, Miss, Ms, Dr. etc	**First Name(s):**	**Surname:**
Job Title:		
Address:		
City, town:	**County:**	
Post code:	**Country:**	
Phone Number:	**Fax Number:**	
Email address:		

Female patient information

Patient ID:	**Age:**	**Date of Birth:**	DD	MM	YYYY

Female partner of male patient information

Patient ID:	**Age:**	**Date of Birth:**	DD	MM	YYYY

Exposure of a pregnant female - not patient or partner Patient

Patient ID:	**Age:**	**Date of Birth:**	DD	MM	YYYY

Treatment information: LENALIDOMIDE SPC®

Batch No.:		**Expiry Date:**			**Dose:**			**Frequency:**	
Start Date:	DD	MM	YYYY		**Stop date:**	DD	MM	YYYY	
Indication for use:									

Menses information Pregnancy

Date of last menses:	DD	MM	YYYY		**Regular menses: No?**	TICK	**Yes?** TICK

Information

Has the pregnancy been confirmed?	**No?**	TICK	**Yes?**	TICK
Estimated gestational stage:	**Estimated date of delivery:**	DD	MM	YYYY
Has the patient already been referred to an obstetrician/gynaecologist?	**No?**	TICK	**Yes?**	TICK

If yes, please specify his/her name and contact detail

Name:	**Contact:**

Reporter

Signature:		**Date:**	DD	MM	YYYY

Background Information on Reason For Pregnancy

		Yes	No
Was patient erroneously considered not to be of child bearing potential			
If yes, state reason for considering not to be of childbearing potential			
a.	Age < 50 ³ years and naturally amenorrhoeic* for < 1 ³ year * amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential		
b.	Premature ovarian failure confirmed by a specialist gynaecologist		
c.	Previous bilateral salpingo-oophorectomy, or hysterectomy		
d.	XY genotype, Turner syndrome, uterine agenesis.		
Indicate from the list below what contraception was used			
a.	Implant		
b.	Levonorgestrel-releasing intrauterine system (IUS)		
c.	Medroxyprogesterone acetate depot		
d.	Tubal sterilization (specify below)		
	I. Tubal ligation		
	II. Tubal diathermy		
	III. Tubal clips		
e.	Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses		
f.	Ovulation inhibitory progesterone-only pills (i.e., desogestrel)		
g.	Other progesterone-only pills		
h.	Combined oral contraceptive pill		
i.	Other intra-uterine devices		
j.	Condoms		
k.	Cervical cap		
l.	Sponge		
m.	Withdrawal		
n.	Other		
o.	None		

Indicate from the list below the reason for contraceptive failure		
Missed oral contraception		
Other medication or intercurrent illness interacting with oral contraception		
Identified mishap with barrier method		
Unknown		
Had the patient committed to complete and continuous abstinence		
Was lenalidomide started despite patient already being pregnant		
Did patient receive educational materials on the potential risk of teratogenicity		
Did patient receive instructions on need to avoid pregnancy		

Prenatal Information

Date of last menstrual period:	Estimated Delivery Date:

PREGNANCY TEST	REFERENCE RANGE	DATE
Urine Qualitative		
Serum quantitative		

Past Obstretic History

Year of pregnancy	Outcome					
	Spontaneous abortion	Therapeutic abortion	Live birth	Still birth	Gestational Age	Type of delivery

Birth Defects

	Yes	No	Unknown
Was there any birth defect from any pregnancy			
Is there any family history of any congenital abnormality abstinence			
If yes to either of these questions, please provide details below:			

Maternal Past Medical History

Condition	Dates	Treatment	Outcome	
	From	To		

Maternal Current Medical Conditions

Condition	From	Treatment

Maternal Social History

	Yes	No
Alcohol		
If yes, amount/units per day:		
Tobacco		
If yes, amount per day:		
IV or recreational drug use		
If yes, provide details		

MATERNAL MEDICATION DURING PREGNANCY AND IN 4 WEEKS BEFORE PREGNANCY
(including herbal, alternative and over the counter medicines and dietary supplements)

Medication/treatment	Start Date	Stop Date/Continuing	Indication

Name of person completing this form	Signature	Date

**** This form based on the brand***

Lenalidomide 5mg, 10mg and 25mg SPC Hard Capsules PIL

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LENALIDOMIDE SPC® is and what it is used for

What LENALIDOMIDE SPC® is

LENALIDOMIDE SPC® capsules contains the active substance 'lenalidomide'. This medicine belongs to a group of medicines which affect how your immune system works. These include some types of cancer.

What LENALIDOMIDE SPC® is used for

LENALIDOMIDE SPC® is a treatment for:

1. Multiple myeloma
2. Myelodysplastic syndromes (MDS)
3. Mantle cell lymphoma (MCL)

Multiple myeloma

Multiple myeloma is a type of cancer which affects a certain kind of white blood cell, called the plasma cell. These cells collect in the bone marrow and divide, becoming out of control. This can damage the bones and kidneys. Multiple myeloma generally cannot be cured. However, the signs and symptoms can be greatly reduced or disappear for a period of time. This is called a 'response'.

Newly diagnosed multiple myeloma – in patients who have had a bone marrow transplant LENALIDOMIDE SPC® is used on its own as maintenance therapy after patients have recovered enough following a bone marrow transplant.

Newly diagnosed multiple myeloma – in patients who cannot have a bone marrow transplant LENALIDOMIDE SPC® is taken with other medicines:

- an anti-inflammatory medicine called 'dexamethasone'
- a chemotherapy medicine called 'melphalan' and
- an immunosuppressant medicine called 'prednisone'.

You will take these other medicines at the start of treatment and then continue to take LENALIDOMIDE SPC® on its own. If you are aged 75 years or older or have moderate to severe kidney problems - your doctor will check you carefully before starting treatment.

Multiple myeloma – in patients who have had treatment before LENALIDOMIDE SPC® is taken together with an anti-inflammatory medicine called 'dexamethasone'. LENALIDOMIDE SPC® can stop the signs and symptoms of multiple myeloma getting worse. It has also been shown to delay multiple myeloma from coming back following treatment.

Myelodysplastic syndromes MDS are a collection of many different blood and bone marrow diseases. The blood cells become abnormal and do not function properly. Patients can experience a variety of signs and symptoms including a low red blood cell count (anemia), the need for a blood transfusion, and be at risk of infection.

LENALIDOMIDE SPC® is used alone to treat adult patients who have been diagnosed with MDS, when all of the following apply:

- you need regular blood transfusions to treat low levels of red blood cells ('transfusion- dependent anemia')
- you have an abnormality of cells in the bone marrow called an 'isolated deletion 5q cytogenetic abnormality'. This means your body does not make enough healthy blood cells
- other treatments have been used before, are not suitable or do not work well enough.
- LENALIDOMIDE SPC® can increase the number of healthy red blood cells that the body produces by reducing the number of abnormal cells:
- this can reduce the number of blood transfusions needed.

It is possible that no transfusions will be needed.

Mantle cell lymphoma MCL is a cancer of part of the immune system (the lymph tissue). It affects a type of white blood cell called 'B-lymphocytes' or B-cells. MCL is a disease where B-cells grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

LENALIDOMIDE SPC® is used alone to treat adult patients who have previously been treated with other medicines.

How LENALIDOMIDE SPC® works

LENALIDOMIDE SPC® works by affecting the body's immune system and directly attacking the cancer. It works in a number of different ways:

- by stopping the cancer cells developing
- by stopping blood vessels growing in the cancer
- by stimulating part of the immune system to attack the cancer cells

2. What you need to know before you take LENALIDOMIDE SPC®

Do not take LENALIDOMIDE SPC®:

- if you are pregnant, think you may be pregnant or are planning to become pregnant, as LENALIDOMIDE SPC® is expected to be harmful to an unborn child (see section 2, 'Pregnancy, breast-feeding and contraception – information for women and men').
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2, 'Pregnancy, breast-feeding and contraception – information for women and men'). If you are able to become pregnant, your doctor will record with each prescription that the necessary measures have been taken and provide you with this confirmation.
- if you are allergic to LENALIDOMIDE SPC® or any of the other ingredients of this medicine listed in section 6. If you think you may be allergic, ask your doctor for advice. If any of these apply to you, do not take LENALIDOMIDE SPC®. Talk to your doctor if you are not sure.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking LENALIDOMIDE SPC® if:

- you have had blood clots in the past - you have an increased risk of developing blood clots in the veins and arteries during treatment
- you have any signs of an infection, such as a cough or fever
- you have or have ever had previous viral infection, particularly hepatitis B infection, varicella zona, HIV. If you are in doubt, talk to your doctor. Treatment with LENALIDOMIDE SPC® may cause virus to become active again, in patients who carry the virus, resulting in a recurrence of the infection. Your doctor should check whether you have ever had hepatitis B infection
- you have kidney problems - your doctor may adjust your dose of LENALIDOMIDE SPC®
- you have had a heart attack, have ever had a blood clot, or if you smoke, have high blood pressure or high cholesterol levels
- you have had an allergic reaction whilst taking thalidomide (another medicine used to treat multiple myeloma) such as rash, itching, swelling, dizziness or trouble breathing
- you have experienced in the past a combination of any of the following symptoms: rash on face or extended rash, red skin, high fever, flu-like symptoms, enlarged lymph nodes (signs of severe skin reaction called drug reaction with eosinophilia and Systemic Symptoms (DRESS), see also section 4 "Possible side effects").
- Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.
- Lenalidomide induced in monkeys malformations similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.
- The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

If any of the above apply to you, tell your doctor before starting treatment.

If you have MDS, you may be more likely to get a more advanced condition called acute myeloid leukaemia (AML). In addition, it is not known how LENALIDOMIDE SPC® affects the chances of you getting AML. Your doctor may therefore do tests to check for signs which may better predict the likelihood of you getting AML during your treatment with LENALIDOMIDE SPC®.

Tests and checks

Before and during the treatment with LENALIDOMIDE SPC® you will have regular blood tests as LENALIDOMIDE SPC® may cause a fall in the blood cells that help fight infection (white blood cells) and help the blood to clot (platelets).

Your doctor will ask you to have a blood test:

- Before treatment
- Every week for the first 8 weeks of treatment
- Then at least every month after that.

For patients with MCL taking LENALIDOMIDE SPC®

Your doctor will ask you to have a blood test:

- Before treatment
- Every week for the first 8 weeks (2 cycles) of treatment
- Then every 2 weeks in Cycles 3 and 4 (see Section 3 'Treatment cycle' for more information)
- after this it will happen at the start of each cycle and
- At least every month

Your doctor may check if you have a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure (this condition is called 'Tumour Lysis Syndrome'). Your doctor may check you for changes to your skin such as red spots or rashes.

Your doctor may adjust your dose of LENALIDOMIDE SPC® or stop your treatment based on the results of your blood tests and on your general condition. If you are newly diagnosed, your doctor may also assess your treatment based on your age and other conditions you already have.

Blood donation

You should not donate blood during treatment and for 4 week after the end of treatment.

Children and adolescents
LENALIDOMIDE SPC® is not recommended for use in children and adolescents under 18 years.

Elderly and people with kidney problems

If you are aged 75 years or older or have moderate to severe kidney problems - your doctor will check you carefully before starting treatment.

Other medicines and LENALIDOMIDE SPC®

Tell your doctor or nurse if you are taking or have recently taken any other medicines. This is because LENALIDOMIDE SPC® can affect the way some other medicines work. Also, some other medicines can affect the way LENALIDOMIDE SPC® works. In particular, tell your doctor or nurse if you are taking any of the following medicines:

- some medicines used to prevent pregnancy such as oral contraceptives, as they may stop working
- some medicines used for heart problems – such as digoxin
- some medicines used to thin the blood – such as warfarin Pregnancy, breast-feeding and contraception - information for women and men

Pregnancy, breast-feeding and contraception - information for women and men

Pregnancy

For women taking LENALIDOMIDE SPC®

- You must not take LENALIDOMIDE SPC® if you are pregnant, as it is expected to be harmful to an unborn baby.
- You must not become pregnant while taking LENALIDOMIDE SPC®. therefore, you must use effective methods of contraception if you are a woman of childbearing potential (see 'Contraception' below).
- If you do become pregnant during your treatment with LENALIDOMIDE SPC®, you must stop the treatment and inform your doctor immediately.

For men taking LENALIDOMIDE SPC®

- If your partner becomes pregnant whilst you are taking LENALIDOMIDE SPC®, you should inform your doctor immediately.
- It is recommended that your partner seeks medical advice.
- You must also use effective methods of contraception (see 'Contraception' below).

Breast-feeding

You must not breast-feed when taking LENALIDOMIDE SPC®, as it is not known if LENALIDOMIDE SPC® passes into human milk.

Contraception

For women taking LENALIDOMIDE SPC® Before starting the treatment, ask your doctor if you are able to become pregnant, even if you think this is unlikely.

If you are able to become pregnant

- you will have pregnancy tests under the supervision of your doctor (before every treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except where it has been confirmed that the fallopian tubes have been severed and sealed, to stop eggs from reaching the uterus (tubal sterilisation) AND

- you must use effective methods of contraception for 4 weeks before starting treatment, during treatment, and until 4 weeks after stopping treatment.

Your doctor will advise you on appropriate methods of contraception.

For men taking LENALIDOMIDE SPC®

LENALIDOMIDE SPC® passes into human semen. If your female partner is pregnant or able to become pregnant, and she does not use effective methods of contraception, you must use condoms during treatment and 1 week after the end of treatment, even if you have had a vasectomy.

Driving and using machines

Do not drive or operate machines if you feel dizzy, tired, sleepy, have vertigo or blurred vision after taking LENALIDOMIDE SPC®.

LENALIDOMIDE SPC® contains lactose

LENALIDOMIDE SPC® contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take LENALIDOMIDE SPC®

LENALIDOMIDE SPC® must be given to you by healthcare professionals with experience in treating multiple myeloma, MDS or MCL.

- When LENALIDOMIDE SPC® is used to treat multiple myeloma in patients who cannot have a bone marrow transplant or have had other treatments before, it is taken with other medicines (see section 1 'What Lenalidomide is used for').

- When LENALIDOMIDE SPC® is used to treat multiple myeloma in patients who have had a bone marrow transplant or to treat patients with MDS or MCL, it is taken alone.

Always take LENALIDOMIDE SPC® exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. If you are taking Lenalidomide in combination with other medicines, you should refer to the package leaflets for these medicines for further information on their use and effects.

Treatment cycle LENALIDOMIDE SPC® is taken on certain days over 4 weeks (28 days). • Each 28 days is called a 'treatment cycle'. • Depending on the day of the cycle, you will take one or more of the medicines. However, on some days you do not take any of the medicines. • After completing each 28-day cycle, you should start a new 'cycle' over the next 28 days.

Sample 28-day dosing cycle

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

Take REVLIMID 25 mg every day for 21 days, as shown

Take dexamethasone 40 mg on days 1, 8, 15, and 22, as shown*

Do not take REVLIMID or dexamethasone on days 23–28

How much LENALIDOMIDE SPC® to take

Before you start treatment, your doctor will tell you:

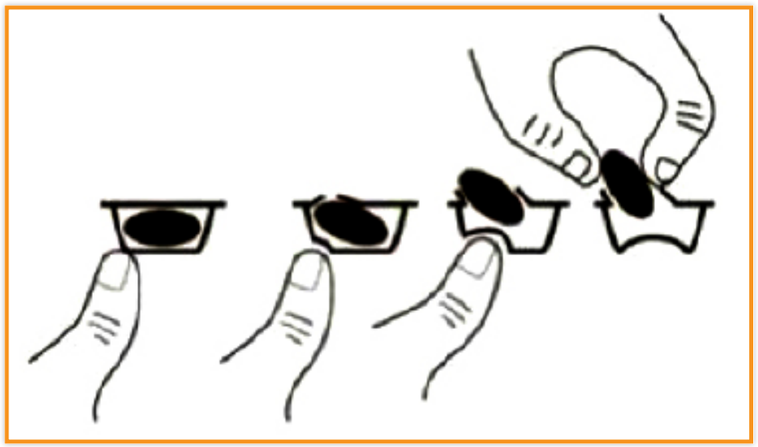
- how much LENALIDOMIDE SPC® you should take
- how much of the other medicines you should take in combination with LENALIDOMIDE SPC® if any
- on what days of your treatment cycle to take each medicine

How and when to take LENALIDOMIDE SPC®

- swallow the capsules whole, preferably with water.
- do not break, open or chew the capsules. If powder from a broken LENALIDOMIDE SPC® capsule makes contact with the skin, wash the skin immediately and thoroughly with soap and water.
- the capsules can be taken either with or without food.
- you should take LENALIDOMIDE SPC® at about the same time on the scheduled days.

Taking this medicine to remove the capsule from the blister:

- press only one end of the capsule out to push it through the foil
- do not put pressure on the centre of the capsule, as this can cause it to break.



Duration of the treatment with LENALIDOMIDE SPC®

LENALIDOMIDE SPC® is taken in treatment cycles, each cycle lasting 28 days (see above 'Treatment cycle'). You should continue the cycles of treatment until your doctor tells you to stop.

If you miss a dose of Lenalidomide SPC, and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do not take 2 doses at the same time.

Take your next capsule at the usual time the next day. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, LENALIDOMIDE SPC® can cause side effects, although not everybody gets them.

Serious side effects which may affect more than 1 in 10 people (very common)

LENALIDOMIDE SPC® may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders such as nosebleeds and bruising.

LENALIDOMIDE SPC® may also cause blood clots in the veins (thrombosis). Therefore you must tell your doctor immediately if you experience:

- fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection including within the bloodstream (sepsis)
- bleeding or bruising in the absence of injury
- chest pain or leg pain
- shortness of breath

Other side effects

It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with LENALIDOMIDE SPC® treatment, therefore your doctor should carefully evaluate the benefit and risk when you are prescribed LENALIDOMIDE SPC®.

Very common side effects (may affect more than 1 in 10 people):

- A fall in the number of red blood cells which may cause anemia leading to tiredness and weakness
- Constipation, diarrhoea, nausea, redness of skin, rashes, vomiting, muscle cramps, muscle aches, bone pain, joint pain, tiredness, generalised swelling including swelling of your arms and legs
- Fever and flu like symptoms including fever, muscle ache, headache, earache and chills
- Numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor, changes in the way things taste
- Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting, which may be symptoms of a heart attack (myocardial infarction)
- Decreased appetite
- Low levels of potassium in the blood
- Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism)
- Infections of all types
- Infection of the lung and the upper respiratory tract, shortness of breath
- Blurred vision
- Clouding of your eye (cataract)
- Kidney problems
- Changes to a protein in the blood that can cause swelling of the arteries (vasculitis)
- Increases in your blood sugar level (diabetes)
- Headache
- Dry skin
- Stomach pain
- Mood change, difficulty sleeping

Common side effects (may affect up to 1 in 10 people):

- Infection of the sinuses that surround the nose
- Bleeding from the gums, stomach, or bowels
- Increase in pain, tumour size, redness around the tumour
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Darkening of your skin
- Skin eruptions, skin cracking, flaking or peeling skin
- Hives, itching, increased sweating, dehydration
- Sore inflamed mouth, dry mouth, difficulty swallowing
- Heartburn
- Production of much more or much less urine than usual (which may be a symptom of kidney failure), passing blood in the urine
- Shortness of breath especially when lying down (which may be a symptoms of heart failure)
- Difficulty getting an erection
- Stroke, fainting
- Muscle weakness
- Joint swelling
- Changes to blood thyroid hormone, low levels of calcium, phosphate or magnesium in the blood Depression
- Deafness
- Abnormal liver test results
- Impaired balance, difficulty moving
- Ringing in the ears (tinnitus)
- An excess of iron in the body
- Thirst
- Confusion
- Toothache
- Weight loss

Uncommon side effects (may affect up to 1 in 100 people):

- Bleeding within the skull
- Circulatory problems
- Loss of vision
- Loss of sex drive (libido)
- Passing large amount of urine with bone pain and weakness, which may be symptoms of a kidney disorder (Fanconi syndrome) Stomach pain, bloating, or diarrhoea, which may be symptoms of inflammation in the large intestine (called colitis or caecitis)
- Passing much more or much less urine than usual, which may be a symptom of a type of kidney problem (called renal tubular necrosis)
- Changes to the colour of your skin, sensitivity to sunlight
- Certain types of skin tumour
- Hives, rashes, swelling of eyes, mouth or face, difficulty breathing, or itching, which may be symptoms of an allergic reaction

Rare side effects (may affect up to 1 in 1,000 people):

- Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).
- Tumor lysis syndrome - metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heartbeat, seizures, and sometimes death.

Not known (frequency cannot be estimated from the available data):

- Sudden, or mild but worsening pain in the upper stomach and/or back, which remains for a few days, possibly accompanied by nausea, vomiting, fever and a rapid pulse. These symptoms may be due to inflammation of the pancreas.
- Wheezing, shortness of breath or a dry cough, which may be symptoms caused by inflammation of the tissue in the lungs.
- Yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale colored stools, dark colored urine, skin itch, rash, pain or swelling of the stomach –these may be symptoms of injury to the liver (hepatic disorder).
- Rare cases of muscle breakdown (muscle pain, weakness or swelling) which can lead to kidney problems (rhabdomyolysis) have been observed, some of them when LENALIDOMIDE SPC® is administered with a statin (a type of cholesterol lowering medicines).
- A condition affecting the skin caused by inflammation of small blood vessels, along with pain in the joints and fever (leukocytoclastic vasculitis).
- Breakdown of the wall of the stomach or gut. This may lead to very serious infection. Tell your doctor if you have severe stomach pain, fever, nausea, vomiting, blood in your stool, or changes in bowel habits.
- Viral infections, including herpes zoster (also known as 'shingles', a viral disease that causes a painful skin rash with blisters) and recurrence of hepatitis B infection (which can cause yellowing of the skin and eyes, dark brown-colored urine, right-sided stomach pain, fever and feeling nauseous or being sick).
- Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome). Stop using LENALIDOMIDE SPC® if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side affects you can help provide more information on the safety of this medicine.

5. How to store LENALIDOMIDE SPC®

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and on the carton after 'EXP'. The expiry date refers to the last day of that month.

- This product does not require any special storage conditions.
- Do not use this medicine if you notice any damage or signs of tampering to the pack.
- Do not throw away any medicines via wastewater or household waste. Please return unused medicines to your pharmacist. These measures will help protect the environment.

6. Contents of the pack and other information

What LENALIDOMIDE SPC® capsules contain

Lenalidomide 5 mg SPC capsules, hard: Each capsule contains 5 mg of Lenalidomide.
Lenalidomide 10 mg SPC capsules, hard: Each capsule contains 10 mg of Lenalidomide.
Lenalidomide 25mg SPC capsules, hard: Each capsule contains 25 mg of Lenalidomide.

What LENALIDOMIDE SPC® capsules look like and contents of the pack

Lenalidomide 5 mg SPC capsules, hard:

White to off-white colored powder filled in size '4' hard gelatin capsules with opaque white colored cap imprinted 'RDY' with black ink and opaque white colored body imprinted '5mg' with black ink.

Lenalidomide 10 mg SPC capsules, hard:

White to off-white colored powder filled in size '2' hard gelatin capsules with pale green colored cap imprinted 'RDY' with black ink and pale-yellow colored body imprinted '10mg' with black ink.

Lenalidomide 25mg SPC capsules, hard:

White to off-white colored powder filled in size '0' hard gelatin capsules with opaque white colored cap imprinted 'RDY' with black ink and opaque white colored body imprinted '25mg' with black ink.

Alu-Alu blisters. Pack size of 7 or 21 capsules. Not all pack sizes may be marketed

MARKETING AUTHORIZATION HOLDER:

Sudair Pharma Company (SPC)
King Fahad road, Building 911- The Ground Floor Riyadh, Saudi Arabia

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Manufacturer
Dr. Reddy's Laboratories Ltd. Formulation Unit VII Plot No. P1 to P9, Phase III, Duvvada, VSEZ, Visakhapatnam, Andhra Pradesh, INDIA - 530 046

This leaflet was last revised in 12/2017

To report any side effect(s):

SAUDI ARABIA

The National Pharmacovigilance and Drug Safety Centre (NPC)
Fax: **+966 11 205 7662**
Call NPC: **+966 11 20 38222** **Ext's: 2317 _ 2356 _ 2353 _ 2354 _ 2334 _ 2340**
Toll free phone: **800 249 0000**
E-mail: **npc.drug@sfda.gov.sa**
Website: **www.sfda.gov.sa/npc**

OTHER GCC STATES

Please contact the relevant competent authority.

Council of Arab Health Ministers

The following statements issued by the Council of Arab Health Ministers should be printed in the PIL.

This is a Medicament

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers Union of Arab Pharmacists

Summary Of Product Characteristics

Summary Of Product Characteristics

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lenalidomide 5 mg capsules, hard
Lenalidomide 10 mg capsules, hard
Lenalidomide 25mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lenalidomide 5 mg capsules, hard
Each capsule contains 5 mg of Lenalidomide.

Lenalidomide 10 mg capsules, hard
Each capsule contains 10 mg of Lenalidomide.

Lenalidomide 25mg capsules, hard
Each capsule contains 25 mg of Lenalidomide.

3. PHARMACEUTICAL FORM

Hard capsule.

Lenalidomide 5 mg capsules, hard:
White to off-white colored powder filled in size ‘4’ hard gelatin capsules with opaque white colored cap imprinted ‘RDY’ with black ink and opaque white colored body imprinted ‘5mg’ with black ink.

Lenalidomide 10 mg capsules, hard:
White to off-white colored powder filled in size ‘2’ hard gelatin capsules with pale green colored cap imprinted ‘RDY’ with black ink and pale yellow colored body imprinted ‘10mg’ with black ink.

Lenalidomide 25mg capsules, hard:
White to off-white colored powder filled in size ‘0’ hard gelatin capsules with opaque white colored cap imprinted ‘RDY’ with black ink and opaque white colored body imprinted ‘25mg’ with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Lenalidomide as combination therapy is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

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

Myelodysplastic syndromes
Lenalidomide is indicated for the treatment of 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.

Mantle cell lymphoma
Lenalidomide is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma

4.2 Posology and method of administration

Lenalidomide treatment should be supervised by a physician experienced in the use of anti- cancer therapies.

For all indications described below:

- Dose is modified based upon clinical and laboratory findings.
- Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
- In case of neutropenia, the use of growth factors in patient management should be considered.
- If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Posology
Newly diagnosed multiple myeloma (NDMM)

Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

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

	Starting dose (10 mg)	If dose increased (15 mg) [a]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (days 1-21 every 28 days)	5 mg
Dose level -3	Not applicable	5 mg (days 1-21 every 28 days)
	Do not dose below 5 mg (days 1-21 every 28 days)	

**** After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.***

Thrombocytopenia

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level once daily

Neutropenia

When neutrophils	Recommended course[a]
Fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily

****At the physician›s discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.***

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 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

	Lenalidomide[a]	Dexamethasone
Starting dose	25 mg	40 mg
Dose level -1	20 mg	20 mg
Dose level -2	15 mg	12 mg
Dose level -3	10 mg	8 mg
Dose level- 4	5 mg	4 mg
Dose level -5	2.5 mg	NA

**** Dose reduction for both products can be managed independently***

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

**** If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.***

Neutropenia

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose- dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥1,5 x 109/L with a platelet count ≥ 100 x 109/L at the beginning of a new cycle).

Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28- day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day

cycles, prednisone 2 mg/kg orally on days 1-4 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 alone,10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression.

Dose reduction steps

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose level -2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose level -3	2.5 mg	NA	0.25 mg/kg

**** If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide***

Thrombocytopenia

When platelets	Recommended course
First fall to < 25 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/L	Resume lenalidomide and melphalan at Dose level -1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily.

Neutropenia

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L[a]	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose- dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

**** If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.***

Multiple myeloma with at least one prior therapy

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days.

Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Dose reduction steps

Starting dose	25 mg
Dose level -1	15 mg
Dose level -2	10 mg
Dose level -3	5 mg

Thrombocytopenia

When platelets	Recommended course
First fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at Dose level 1-
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level 2- or 3-) once daily. Do not dose below 5 mg once daily.

Neutropenia

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose- dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.

Myelodysplastic syndromes (MDS)

Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L and/or platelet counts < 25 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles.

Dose reduction steps

Starting dose	10 mg once daily on days 1-21 every 28 days
Dose level -1	5.0 mg once daily on days 1-28 every 28 days
Dose level -2	2.5 mg once daily on days 1-28 every 28 days
Dose level -3	2.5 mg every other day 1-28 every 28 days

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 25 x 109/L - < 50 x 10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/L at any time	Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)

Neutropenia

When neutrophils	Recommended course
Fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Mantle cell lymphoma

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles.

Dose reduction steps

Starting dose	25 mg once daily on days 1-21, every 28 days
Dose Level -1	20 mg once daily on days 1-21, every 28 days
Dose Level -2	15 mg once daily on days 1-21, every 28 days
Dose Level -3	10 mg once daily on days 1-21, every 28 days
Dose Level -4	5 mg once daily on days 1-21, every 28 days
Dose Level -5	2.5 mg once daily on days 1-21, every 28 days[1] 5 mg every other day on days 1-21, every 28 days

[1] ***- In countries where the 2.5 mg capsule is available.***

Thrombocytopenia

When platelets	Recommended Course
Fall to < 50 x 10^9/L	Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days
Return to ≥ 60 x 10^9/L	Resume lenalidomide at next lower level (Dose Level -1)
For each subsequent drop below 50 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥60 x 10^9/L	Resume lenalidomide at next lower level (Dose Level -2, -3, -4 or -5). Do not dose below Dose Level -5

Neutropenia

When neutrophils	Recommended Course
Fall to < 1 x 10^9/L for at least 7 days or Falls to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥ 1 x 10^9/L	Resume lenalidomide at next lower dose level (Dose Level -1)
For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥1 x 10^9/L	Resume Lenalidomide at next lower dose level (Dose Level -2, -3, -4, -5). Do not dose below Dose Level -5

Tumour flare reaction

Lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician›s discretion. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR

All indications

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician›s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population

Lenalidomide should not be used in children and adolescents from birth to less than 18 years because of safety concerns.

Elderly

Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age and in myelodysplastic syndromes patients up to 95 years of age and and in mantle cell lymphoma patients up to 88 years of age.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Newly diagnosed multiple myeloma: patients who are not eligible for transplant

Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered.

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

No dose adjustment is proposed for patients older than 75 years who are treated with lenalidomide in combination with melphalan and prednisone.

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation.

Lenalidomide combined therapy was less tolerated in newly diagnosed multiple myeloma patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years.

Multiple myeloma: Patients with at least one prior therapy

The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

Myelodysplastic syndromes

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Mantle cell lymphoma

For mantle cell lymphoma patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged 65 years or over compared with patients aged under 65 years of age.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance. Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma or myelodysplastic syndromes or mantle cell lymphoma.

The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.

There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

Multiple myeloma

Renal function (CLcr)	Dose adjustment (Days 1 to 21 of repeated 28- day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily1
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily2 15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis.

[1] ***The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.***

[2] ***In countries where the 7.5 mg capsule is available.***

Myelodysplastic syndromes

Renal function (CLcr)	Dose adjustment	
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg once daily (days 1-28 of repeated 28-day cycles)

	Dose level -2*	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

**** Recommended dose reduction steps during treatment and restart of treatment to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide, as described above.***

Mantle cell lymphoma

Renal function (CLcr)	Dose adjustment (Days 1-21 of repeated 28- day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily1
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily2 15 mg every other day

[1] ***The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.***

[2] ***In countries where the 7.5 mg capsule is available.***

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

Patients with hepatic impairment

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Method of administration Oral use.

Lenalidomide capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

4.4 Special warnings and precautions for use

Pregnancy warning

Lenalidomide is Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-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 lactation does not rule out childbearing potential.

Counselling

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

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.
- For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject. As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose

interruptions and/or cessation of treatment.

- Understand that if his female partner becomes pregnant whilst he is taking lenalidomide or shortly after he has stopped taking lenalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.
- The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be 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 in combination therapy, and to a lesser extent in patients with myelodysplastic syndromes 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 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing

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

Prior to starting treatment

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

Follow-up and end of treatment

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

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders Myocardial infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with lenalidomide monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) than in patients with multiple myeloma treated with lenalidomide in combination therapy.

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone. The risk of ATE is lower in patients with multiple myeloma treated with lenalidomide monotherapy than in patients with multiple myeloma treated with lenalidomide in combination therapy.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient›s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy

started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Neutropenia and thrombocytopenia

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required.

In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes.

Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding

Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance

The adverse reactions from CALGB 100104 included events reported post-high dose melphalan and ASCT (HDM/ASCT) as well as events from the maintenance treatment period. A second analysis identified events that occurred after the start of maintenance treatment. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

Overall, grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reductions may be required.

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding, Haemorrhagic disorders).

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm. Patients should be advised to promptly report febrile episodes and dose reductions may be required.

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding.

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients)

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding

Multiple myeloma: patients with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone- treated patients; Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients.

Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo.

Mantle cell lymphoma

Lenalidomide treatment in mantle cell lymphoma patients is associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm

Thyroid disorders

Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

Tumour flare reaction and tumour lysis syndrome

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.

Tumour burden

Mantle cell lymphoma

Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available.

Early death

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, there were 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (40%) and 6/28 (21%).

Adverse events

In study MCL-002, during treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).

Patients with high tumour burden should therefore be closely monitored for adverse reactions including signs of tumour flare reaction (TFR). Please refer to posology for dose adjustments for TFR. High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tumour flare reaction

Mantle cell lymphoma

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti- inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient.

Allergic reactions

Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide. Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions

Severe cutaneous reactions including SJS, and TEN and DRESS have been reported with the use of lenalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance

Lenalidomidecapsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Second primary malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

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).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Lenalidomidein this setting.

The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin›s lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person- years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

Karyotype

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Lenalidomide when MDS is associated with Del (5q) and complex cytogenetics is unknown.

TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC- p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038)

Progression to other malignancies in mantle cell lymphoma

In mantle cell lymphoma, AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are potential risks.

Hepatic disorders

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

Infection with or without neutropenia

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT in patients with NDMM who are not eligible for transplant, and with lenalidomide maintenance compared to placebo in patients with NDMM who had undergone ASCT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Cases of viral reactivation have been reported in patients receiving lenalidomide, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

Some of the cases of viral reactivation had a fatal outcome.

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster requiring a temporary hold or permanent discontinuation of the treatment with lenalidomide and adequate antiviral treatment.

Reactivation of hepatitis B has been reported rarely in patients receiving lenalidomide who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure resulting in discontinuation of lenalidomide and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when lenalidomide is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Newly diagnosed multiple myeloma patients

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min.

Cataract

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

4.5 Interaction With Other Medicinal Products And Other Forms Of Interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken

Warfarin
Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin
Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

Statins
There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).

Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P- gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Due to the teratogenic potential, lenalidomide must be prescribed under a Pregnancy Prevention Programme unless there is reliable evidence that the patient does not have childbearing potential.

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject. As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.

Breast-feeding
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance

A conservative approach was applied to determine the adverse reactions from CALGB 100104. The adverse reactions described in Table 1 included events reported post-HDM/ASCT as well as events from the maintenance treatment period.

A second analysis that identified events that occurred after the start of maintenance treatment suggests that the frequencies described in Table below may be higher than actually observed during the maintenance treatment period. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

The serious adverse reactions observed more frequently (≥5%) with lenalidomide maintenance than placebo were:

- Pneumonias (10.6%; combined term) from IFM 2005-02
- Lung infection (9.4% [9.4% after the start of maintenance treatment]) from CALGB 100104

In the IFM 2005-02 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (60.8%), bronchitis (47.4%), diarrhoea (38.9%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), asthenia (29.7%), cough (27.3%), thrombocytopenia (23.5%), gastroenteritis (22.5%) and pyrexia (20.5%).

In the CALGB 100104 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (79.0% [71.9% after the start of maintenance treatment]), thrombocytopenia (72.3% [61.6%]), diarrhoea (54.5% [46.4%]), rash (31.7% [25.0%]), upper respiratory tract infection (26.8% [26.8%]), fatigue (22.8% [17.9%]), leucopenia (22.8% [18.8%]) and anemia (21.0% [13.8%]).

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan, prednisone and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma: patients with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Grade 4 neutropenia

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Lenalidomidein patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study. In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide. Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia.

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Mantle cell lymphoma

The overall safety profile of Lenalidomidein patients with mantle cell lymphoma is based on data from 254 patients from a Phase II randomized, controlled study MCL-002.

Additionally, ADRs from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in Study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were:

- Neutropenia (3.6%)
- Pulmonary embolism (3.6%)
- Diarrhoea (3.6%)

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in Study MCL-002 were neutropenia (50.9%), anaemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%).

During treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).

High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tabulated list of adverse reactions

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Tabulated summary for monotherapy in MM

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the longer duration of treatment in the lenalidomide-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies.

Table 1. *ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone*

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonias◊, a, Upper respiratory tract infection, Neutropenic infection, Bronchitis◊, Influenza◊, Gastroenteritis◊, Sinusitis, Nasopharyngitis, Rhinitis Common Infection◊, Urinary tract infection◊*, Lower respiratory tract infection, Lung infection	Very Common Pneumonias◊, a, Neutropenic infection Common Sepsis◊, b, Bacteraemia, Lung infection◊, Lower respiratory tract infection bacterial, Bronchitis◊, Influenza◊, Gastroenteritis◊, Herpes zoster◊, Infection◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome◊*	
Blood and Lymphatic System Disorders	Very Common Neutropenia^,◊, Febrile neutropenia^,◊, Thrombocytopenia^,◊,, Anemia, Leucopenia◊, Lymphopenia	Very Common Neutropenia^,◊, Febrile neutropenia^,◊, Thrombocytopenia^,◊, Anemia, Leucopenia◊, Lymphopenia Common Pancytopenia◊
Metabolism and Nutrition Disorders	Very Common Hypokalaemia	Common Hypokalaemia, Dehydration
Nervous System Disorders	Very Common Paraesthesia Common Peripheral neuropathyc	Common Headache
Vascular Disorders	Common Pulmonary embolism◊*	Common Deep vein thrombosis^,◊,d
Respiratory, Thoracic and Mediastinal Disorders	Very Common Cough Common Dyspnoea◊, Rhinorrhoea	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash, Dry skin	Common Rash, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms Common Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue, Asthenia

◊ Adverse reactions reported as serious in clinical trials in patients with NDMM who had undergone ASCT

** Applies to serious adverse drug reactions only*

^ See undesirable effects description of selected adverse reactions

[a] "Pneumonias" combined AE term includes the following PTs: Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis

[b] "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis

[c] "Peripheral neuropathy" combined AE term includes the following preferred terms (PTs): Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy

[d] "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis

Tabulated summary for combination therapy in MM

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the longer duration of treatment in the lenalidomide-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies

Table 2. *ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone*

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis Common Sepsis, Sinusitis	Common Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma, Squamous skin cancer^*	Common Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin** Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia^, Thrombocytopenia ^, Anemia, Haemorrhagic disorder ^, Leucopenias Common Febrile neutropenia, Pancytopenia Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia	Very Common Neutropenia^, Thrombocytopenia^, Anemia, Leucopenias Common Febrile neutropenia^, Pancytopenia, Haemolytic anemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity^	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration	Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired	Common Cerebrovascular accident, Dizziness, Syncope Uncommon Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute)^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia
Vascular Disorders	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Hypotension, Hypertension, Ecchymosis^	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea, Epistaxis^	Common Respiratory distress, Dyspnoea
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry mouth, Stomatitis, Dysphagia Uncommon	Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting
	Colitis, Caecitis	
Hepatobiliary Disorders	Common Abnormal liver function tests Uncommon Hepatic failure^	Common Cholestasis, Abnormal liver function tests Uncommon Hepatic failure^
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia Common Muscular weakness, Joint swelling, Myalgia	Common Muscular weakness, Bone pain Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute) Common Haematuria^, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis

Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy	Common Fatigue, Pyrexia, Asthenia
Investigations	Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

^See undesirable effects description of selected adverse reactions

Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

*** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/ dexamethasone compared to controls*

Tabulated summary from monotherapy

The following table are derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes and mantle cell lymphoma.

Table 3. *ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#*

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)	Very Common Pneumonia◊ Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Bronchitis
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^, Neutropenia^, Leucopenias	Very Common Thrombocytopenia^◊, Neutropenia^◊, Leucopenias Common Febrile neutropenia^◊
Endocrine Disorders	Very Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Decreased appetite Common Iron overload, Weight decreased	Common Hyperglycaemia◊, Decreased appetite
Psychiatric Disorders		Common Altered mood◊~
Nervous System Disorders	Very Common Dizziness, Headache Common Paraesthesia	
Cardiac Disorders		Common Acute myocardial infarction^◊, Atrial fibrillation◊, Cardiac failure◊
Vascular Disorders	Common Hypertension, Haematoma	Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Epistaxis^	
Gastrointestinal Disorders	Very Common Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation Common Dry mouth, Dyspepsia	Common Diarrhoea◊, Nausea, Toothache
Hepatobiliary Disorders	Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Dry Skin, Pruritus	Common Rashes, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia	Common Back pain◊
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)	Common Pyrexia
Injury, Poisoning and Procedural Complications		Common Fall

^see description of selected adverse reactions

◊Adverse events reported as serious in myelodysplastic syndromes clinical trials

~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes phase III study; it was not reported as a grade 3 or 4 adverse event

Algorithm applied for inclusion in the SmPC: All ADRs captured by the phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the phase II study algorithm was undertaken and, if the frequency of the ADRs in the phase II study was higher than in the phase III study, the event was included in the EU SmPC at the frequency it occurred in the phase II study.

Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
    - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
    - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
    - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
    - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
    - All treatment-emergent grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
    - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

Table 4. *ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide*

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pneumonia Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Pneumonia◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer^◊, Basal cell Carcinoma◊
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^, Neutropenia^, Leucopenias, Anaemia Common Febrile neutropenia	Very Common Thrombocytopenia^, Neutropenia^◊, Anaemia◊ Common Febrile neutropenia^◊, Leucopenias◊
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation,	Common Dehydration◊, Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System Disorders	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Acute myocardial infarction (including acute)^ ◊, Cardiac failure
Vascular Disorders	Common Hypotension	Common Deep vein thrombosis◊, pulmonary embolism^◊, Hypotension◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoeia	Common Dyspnoeia◊
Gastrointestinal Disorders	Very Common Diarrhoea, Nausea◊, Vomiting◊, Constipation Common Abdominal pain	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough) Common Chills	Common Pyrexia◊, Asthenia◊, Fatigue

^see description of selected adverse reactions

◊Adverse events reported as serious in mantle cell lymphoma clinical trials

Algorithm applied for mantle cell lymphoma:

- Mantle cell lymphoma controlled Phase II study
    - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference in proportion between lenalidomide and control arm
    - All treatment-emergent grade 3 or 4 adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
    - All Serious treatment-emergent adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
- Mantle cell lymphoma single arm Phase II study
    - All treatment-emergent adverse events with ≥ 5% of subjects
    - All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects
    - All Serious treatment-emergent adverse events reported in 2 or more subjects

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 5. *ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide*

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Rare Tumour lysis syndrome
Blood and Lymphatic System Disorders	Not known Acquired haemophilia	
Endocrine Disorders	Common Hyperthyroidism	
Respiratory, Thoracic and Mediastinal Disorders		Not Known Interstitial pneumonitis
Gastrointestinal Disorders		Not Known Pancreatitis, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations) ^
Hepatobiliary Disorders	Not Known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^	Not Known Acute hepatic failure^, Hepatitis toxic^
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ Not Known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms^

^see description of selected adverse reactions

Description of selected adverse reactions

Teratogenicity

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 4 neutropenia compared to placebo maintenance (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively).

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 3 or 4 thrombocytopenia compared to placebo maintenance (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

Multiple myeloma patients with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone- treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

Myelodysplastic syndromes

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

Mantle cell lymphoma

In mantle cell lymphoma patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the Phase II study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm.

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone or as monotherapy in patients with myelodysplastic syndromes treated with lenalidomide monotherapy. Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross- reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second primary malignancies
In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Acute myeloid leukaemia

- Multiple myeloma

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT. This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- Myelodysplastic syndromes

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. The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Lenalidomidein myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported

Tumour flare reaction and tumour lysis syndrome
In Study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all report were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. There were no reports of TLS in study MCL-001

Gastrointestinal disorders
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single- dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacotherapeutic group

Other immunosuppressants. ATC code: L04AX04 Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro- erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide efficacy and safety have been evaluated in five phase III studies in newly diagnosed multiple myeloma, two phase III studies in relapsed refractory multiple myeloma, one phase III study and one phase II study in myelodysplastic syndromes and one phase II study in mantle cell lymphoma as described below.

Newly diagnosed multiple myeloma

Lenalidomide maintenance in patients who have undergone ASCT

The efficacy and safety of lenalidomide maintenance was assessed in two phase 3 multicenter, randomised, double-blind 2-arm, parallel group, placebo-controlled studies: CALGB 100104 and IFM 2005-02

CALGB 100104

Patients between 18 and 70 years of age with active MM requiring treatment and without prior progression after initial therapy were eligible.

Patients were randomised 1:1 within 90-100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on days 1-28 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 primary efficacy endpoint in the study was progression free survival (PFS) from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 460 patients were randomised: 231 patients to Lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

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 in the placebo arm were allowed to cross over to receive lenalidomide before disease progression.

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 17 December 2009 (15.5 months follow up) showed a 62% reduction in risk of disease progression or death favoring lenalidomide (HR = 0.38; 95% CI 0.27, 0.54; p <0.001). The median overall PFS was 33.9 months (95% CI NE, NE) in the lenalidomide arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm.

The PFS benefit was observed both in the subgroup of patients with CR and in the subgroup of patients who had not achieved a CR.

The results for the study, using a cut-off of 1 February 2016, are presented in Table 6

Table 6. *Summary of overall efficacy data*

	Lenalidomide (N = 231)	Placebo (N = 229)
Investigator-assessed PFS		
Mediana PFS time, months (95% CI)b	56.9 (41.9, 71.7)	29,4 (20.7, 35.5)
HR [95% CI]c; p-valued	0.61 (0.48, 0.76); <0.001	
PFS2e		
Mediana PFS2 time, months (95% CI)b	80.2 (63.3, 101.8)	52.8 (41.3, 64.0)
HR [95% CI]c ; p-valued	0.61 (0.48, 0.78); <0.001	
Overall survival		
Mediana OS time, months (95% CI)b	111.0 (101.8, NE)	84.2 (71.0, 102.7)
8-year survival rate, % (SE)	60.9 (3.78)	44.6 (3.98)
HR [95% CI]c ; p-valued	0.61 (0.46, 0.81); <0.001	
Follow-up		
Medianf (min, max), months: all surviving patients	81.9 (0.0, 119.8)	81.0 (4.1, 119.5)

CI = confidence interval; HR = hazard ratio; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival;

a The median is based on the Kaplan-Meier estimate.

b The 95% CI about the median.

c Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

d The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

e Exploratory endpoint (PFS2). Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding was not considered as a second-line therapy.

f Median follow-up post-ASCT for all surviving subjects.

Data cuts: 17 Dec 2009 and 01 Feb 2016

IFM 2005-02

Patients aged < 65 years at diagnosis who had undergone ASCT and had achieved at least a stable disease response at the time of hematologic recovery were eligible. Patients were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on days 1-28 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 1-21 of a 28-day cycle). Treatment was to be continued until disease progression.

The primary endpoint was PFS defined from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 614 patients were randomised: 307 patients to lenalidomide and 307 patients to placebo.

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 SPMs (see Section 4.4).

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 7 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favoring lenalidomide (HR = 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 PFS benefit was less in the subgroup of patients with CR than in the subgroup of patients who had not achieved a CR.

The updated PFS, using a cut-off of 1 February 2016 (96.7 months follow up) continues to show a PFS advantage: HR = 0.57 (95% CI 0.47, 0.68; p < 0.001). The median overall PFS was 44.4 months (39.6, 52.0) in the lenalidomide arm versus 23.8 months (95% CI 21.2, 27.3) in the placebo arm. For PFS2, the observed HR was 0.80 (95% CI 0.66, 0.98; p = 0.026) for lenalidomide versus placebo. The median overall PFS2 was 69.9 months (95% CI 58.1, 80.0) in the lenalidomide arm versus 58.4 months (95% CI 51.1, 65.0) in the placebo arm. For OS, the observed HR was 0.90: (95% CI 0.72, 1.13; p = 0.355) for lenalidomide versus placebo. The median overall survival time was 105.9 months (95% CI 88.8, NE) in the lenalidomide arm versus 88.1 months (95% CI 80.7, 108.4) in the placebo arm.

Lenalidomide in combination with dexamethasone in patients who are not eligible for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a phase III, multicenter, randomised, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the

patient due to cost or other reason.The study (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 melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomised (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomisation by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on days 1 to 21 of 28- day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease- related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 7:

Table 7. *Summary of overall efficacy data*

	Rd	**Rd18**	**MPT**
	(N = 535)	(N = 541)	(N = 547)
Investigator-assessed PFS - (months)			
Mediana PFS time, months (95% CI)b	26.0 (20.7, 29.7)	21.0 (19.7, 22.4)	21.9 (19.8, 23.9)
HR [95% CI]c; p-valued			
Rd vs MPT	0.69 (0.59, 0.80); <0.001		
Rd vs Rd18	0.71 (0.61, 0.83); <0.001		
Rd18 vs MPT	0.99 (0.86, 1.14); 0.866		
PFS2e - (months)			
Mediana PFS2 time, months (95% CI)b	42.9 (38.1, 47.4)	40.0 (36.2, 44.2)	35.0 (30.4, 37.8)
HR [95% CI]c; p-valued			
Rd vs MPT	0.74 (0.63, 0.86); <0.001		
Rd vs Rd18	0.92 (0.78, 1.08); 0.316		
Rd18 vs MPT	0.80 (0.69, 0.93); 0.004		
Overall survival (months)			
Mediana OS time, months (95% CI)b	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI]c; p-valued			
Rd vs MPT	0.75 (0.62, 0.90); 0.002		
Rd vs Rd18	0.91 (0.75, 1.09); 0.305		
Rd18 vs MPT	0.83 (0.69, 0.99); 0.034		
Follow-up (months)			
Medianf (min, max): all patients	40.8 (0.0, 65.9)	40.1 (0.4, 65.7)	38.7 (0.0, 64.2)
Myeloma responseg n (%)			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)
Duration of response - (months)h			
Mediana (95% CI)b	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low- dose dexamethasone; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for 18 cycles; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

a The median is based on the Kaplan-Meier estimate.

b The 95% CI about the median.

c Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

d The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

e Exploratory endpoint (PFS2)

f The median is the univariate statistic without adjusting for censoring.

g Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category, Data cut-off date = 24 May 2013).

h data cut 24 May 2013

Lenalidomide in combination with melphalan and prednisone followed by maintenance therapy in patients who are not eligible for transplant

The safety and efficacy of lenalidomide was assessed in a phase III multicenter, randomised double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared 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. Patients were randomised in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (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; and lenalidomide 10 mg/day orally on days 1 to 21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance therapy starting with lenalidomide 10 mg orally on days 1 to 21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomised to MPR+R, 153 patients randomised to MPR+p and 154 patients randomised to MPp+p. The demographics and disease- related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut-off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 8:

Table 8. *Summary of overall efficacy data*

	MPR+R (N = 152)	**MPR+p (N = 153)**	**MPp +p (N = 154)**
Investigator-assessed PFS - (months)			
Mediana PFS time, months (95% CI)	27.4 (21.3, 35.0)	14.3 (13.2, 15.7)	13.1 (12.0, 14.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.37 (0.27, 0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35, 0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60, 1.01); 0.059		
PFS2 - (months) ¤			
Mediana PFS2 time, months (95% CI)	39.7 (29.2, 48.4)	27.8 (23.1, 33.1)	28.8 (24.3, 33.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.70 (0.54, 0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59, 1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71, 1.19); 0.051		
Overall survival (months)			
Mediana OS time, months (95% CI)	55.9 (49.1, 67.5)	51.9 (43.1, 60.6)	53.9 (47.3, 64.2)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.95 (0.70, 1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65, 1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79, 1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8, 73.8)	46.3 (0.5, 71.9)	50.4 (0.5, 73.3)
Investigator-assessed Myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable (NE)	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed Duration of response (CR+PR) - (months)			
Mediana (95% CI)	26.5 (19.4, 35.8)	12.4 (11.2, 13.9)	12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

a The median is based on the Kaplan-Meier estimate

¤PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomisation to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

Supportive newly diagnosed multiple myeloma studies

An open-label, randomised, multicenter, phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomised to the lenalidomide/low dose dexamethasone arm, and 223 were randomised to the lenalidomide/standard dose dexamethasone arm. Patients randomised to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus dexamethasone 40 mg/day on days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomised to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/ low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two phase III multi-centre, randomised, double- blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on days 1 to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone 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. The dose of dexamethasone was reduced to 40 mg orally once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the len/dex group and 176 in the placebo/dex group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the len/dex group and 175 in the placebo/dex group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that len/dex was statistically significantly superior ($p < 0.00001$) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the len/dex arm were also significantly higher than the placebo/dex arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dex group to receive treatment with the len/dex combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 9 summarizes the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with len/dex (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dex (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with len/dex versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dex. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for len/dex and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dex.

Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the len/dex arm remain significantly higher than in the placebo/dex arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with len/dex versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dex. Despite the fact that 170 out of the 351 patients randomised to placebo/dex received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for len/dex relative to placebo/dex (HR = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 9. *Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)*

Endpoint	**len/dex (N=353)**	**placebo/dex(N=351)**	
Time to event			**HR [95% CI], p-value** [a]
Time to progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001
Progression free survival Median [95% CI], weeks	48.1 [36.4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473], p < 0.001
Overall survival Median [95% CI], weeks 1-year Overall survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0.687, 1.009], p = 0.045
Response rate			**Odds ratio [95% CI], p- value** [b]
Overall response [n, %] Complete response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

[a]: Two-tailed log rank test comparing survival curves between treatment groups. b: Two-tailed continuity-corrected chi-square test.

Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a phase III, multicentre, randomised, double-blind, placebo-controlled, 3- arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS- 003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately.

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 10. *Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS- 003, intent- to-treat populationEndpoint*

	MDS-004 N = 205			**MDS-003 N = 148**
	10 mg[†] N = 69	**5 mg[††] N = 69**	**Placebo* N = 67**	**10 mg N = 148**
Transfusion Independence (≥ 182 days) [#]	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)
Transfusion Independence (≥ 56 days) [#]	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to Transfusion Independence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR[∞]	NR	NR	114.4
Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

[†] Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles

[††] Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles

The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase

[#]Associated with an increase in Hgb of ≥ 1g/dL

[∞] Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

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.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Mantle cell lymphoma

The efficacy and safety of lenalidomide were evaluated in patients with mantle cell lymphoma in a phase II, multicenter, randomised open-label study versus single agent of investigator›s choice in patients who were refractory to their last regimen or had relapsed one to three times (study MCL-002).

Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomised 2:1 to the lenalidomide or the control arm. The investigator›s choice treatment was selected before randomisation and consisted of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.

Lenalidomide was administered orally 25 mg once daily for the first 21 days (D1 to D21) of repeating 28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.

The baseline demographic were comparable between the lenalidomide arm and control arm. Both patient populations presented a median age of 68.5 years with comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number of prior therapies.
The primary efficacy endpoint in study MCL-002 was progression-free survival (PFS).

The efficacy results for the Intent-to-Treat (ITT) population were assessed by the Independent Review Committee (IRC), and are presented in the table below.

Table 11. *Summary of efficacy results – study MCL-002, intent-to-treat population*

	Lenalidomide Arm **N = 170**	**Control Arm** **N = 84**
PFS **PFS, mediana** [95% CI]b (weeks) **Sequential HR** [95% CI]e Sequential log-rank test, p-valuee	37.6 [24.0, 52.6] 0.61 [0.44, 0.84] 0.004	22.7 [15.9, 30.1]
Response[a], n (%) Complete response (CR)	8 (4.7)	0 (0.0)
Partial response (PR) Stable disease (SD)b	60 (35.3) 50 (29.4)	9 (10.7) 44 (52.4)
Progressive disease (PD) Not done/Missing	34 (20.0) 18 (10.6)	26 (31.0) 5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][c] p-valuee	68 (40.0) [32.58, 47.78] < 0.001	9 (10.7)d [5.02, 19.37]
CRR (CR, CRu), n (%) [95% CI][c] p-valuee	8 (4.7) [2.05, 9.06] 0.043	0 (0.0) [95.70, 100.00]
Duration of Response, median[a] [95% CI] (weeks)	69.6 [41.1, 86.7]	45.1 [36.3, 80.9]
Overall Survival **HR** [95% CI][c] Log-rank test, p-value	0.89 [0.62, 1.28] 0.520	

CI = confidence interval; CRR = complete response rate; CR = complete response; CRu = complete response unconfirmed; DMC = Data Monitoring Committee; ITT = intent-to-treat; HR = hazard ratio; KM = Kaplan-Meier; MIPI = Mantle Cell Lymphoma International Prognostic Index; NA = not applicable; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR= partial response; SCT = stem cell transplantation; SD = stable disease; SE = standard error.

[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] The mean and median are the univariate statistics without adjusting for censoring.

[d] The stratification variables included time from diagnosis to first dose (< 3 years and ≥ 3 years), time from last prior systemic anti-lymphoma therapy to first dose (< 6 months and ≥ 6 months), prior SCT (yes or no), and MIPI at baseline (low, intermediate, and high risk).

[e] Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based on the difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CI are presented.

In study MCL-002 in the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. In patients with high tumour burden, corresponding figures were 16/81 (20%) and 2/28 (7%) (see section 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with lenalidomide in all subsets of the paediatric population in multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic Properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption

Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (Cmax) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

Distribution

In vitro (14C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance.

Biotransformation and elimination

Results from human in vitro metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.
In vitro studies indicate that lenalidomide has no inhibitory effect on human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent. At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

Older people

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total lenalidomide clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The Cmax was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session.

Hepatic impairment

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors

Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio- ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline Cellulose Croscarmellose
Sodium
Magnesium Stearate (vegetable grade)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Alu-Alu blisters
Pack size of 7 or 21 capsules. Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water. Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. Marketing authorisation holder

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8. Date of revision of the text

This leaflet was last revised in 10/2018 Version: 00

9. To report any side effects

Saudi Arabia

The National Pharmacovigilance and Drug Safety Centre (NPC)

Fax:	**+966 11 205 7662**		
Call NPC at	**+966 11 203 8222,**	**Ext's:**	**2317 _ 2356 _ 2353 _ 2354 _ 2334 _ 2340**
Toll free phone:	**800 249 0000**		
E-mail:	**npc.drug@sfda.gov.sa**		
Website:	**www.sfda.gov.sa/npc**		

Other GCC States

Please contact the relevant competent authority.

Council of Arab Health Ministers

The following statements issued by the Council of Arab Health Ministers should be printed in the PIL.

This is a Medicament

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

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