i-SECURE Revlimid® (lenalidomide) Risk Management Program

Revlimid® (Lenalidomide)

Dear Healthcare Professional,

Revlimid® (lenalidomide) is a thalidomide analogue and the first in a new class of immunomodulatory drugs known as IMiDs® compounds.

Revlimid® is indicated in the treatment of:
- Multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy
-Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities

Revlimid is structurally related to thalidomide, a known human teratogenic substance that causes severe life-threatening birth defects. Revlimid also induced in monkeys, malformations similar to those described with thalidomide.

If Revlimid is taken during pregnancy, a teratogenic effect of Revlimid in humans is expected.

Therefore, Biologix and Celgene have developed a risk management program for the GCC called i-SECURE (ImiDs Strategy and Education for a Controlled Use of Revlimid and thalidomidE).

Biologix would like to provide you the “i-SECURE Revlimid® Risk Management Program Folder”.

Your folder contains the information and material needed for prescribing and dispensing Revlimid®, including information about the Pregnancy Prevention Program.

It is a requirement of the i-SECURE program that all healthcare professionals ensure that they have read and understood this folder before prescribing or dispensing Revlimid® for patients.

Sincerely,

Biologix FZco

i-SECURE

At a Glance

Revlimid® (Lenalidomide)

Prescriber must

- Complete the "Revlimid Prescriber Registration Form" to enroll in the *i-SECURE* Program
- Complete a "Revlimid Treatment Initiation Form" to register the patient in the *i-SECURE* Program and obtain a Unique Patient Identification Number (UPIN)
- Communicate the benefits and risks of Revlimid therapy to the patient
- Counsel the patient on the risks of exposing an unborn baby to Revlimid, and what the patient must do to minimize this risk
- Provide the patient with a "Revlimid *i-SECURE* Patient Brochure"
- Provide the patient with a completed and signed "Revlimid Prescription Authorization Form" with each Revlimid prescription
- Perform the required scheduled pregnancy testing for females of childbearing potential prior to every prescription
- Remind the patient of the safe use of Revlimid

Pharmacist must

- Complete the "Revlimid Pharmacy Registration Form" to enroll in the *i-SECURE* Program
- Provide counselling to each patient and fill the "Education and Counselling Checklist used by the Registered Pharmacy"
- Check and validate the Revlimid prescription and the "Revlimid Prescription Authorization Form"
- Send the "Revlimid Prescription Authorization Form" and "Education and Counselling Checklist" by email to Biologix at pharmacovigilance@blgx.net
- If all details are verified and approved by Biologix, pharmacy will receive a "Dispense Authorization Form" and dispense
    - No more than a 4-week (28-day) supply of Revlimid per prescription for women of childbearing potential
    - Up to a 12-week (84-day) supply for all other patient categories provided it was so approved by Biologix
- For subsequent prescriptions, verify there are 7 days or less since the last pregnancy test occurred.
- For subsequent prescriptions, verify there are 7 days or less remaining of the 28-day cycles on the existing prescription.

Warning:

Please be informed that your registration in i-SECURE program can be deactivated once any of i-SECURE requirements are not met.

In case of incompliance, Biologix has the right to cease collaboration regarding Revlimid® under i-SECURE.

i-SECURE

At a Glance

Revlimid® (Lenalidomide)

Documents in Revlimid i-*SECURE* Risk Management Program Folder

- Revlimid *i-SECURE* at a Glance
- Revlimid *i-SECURE* Healthcare Professional Information Pack
  - Revlimid Prescriber Registration Form
  - Revlimid Pharmacy Registration Form
  - Education and Counseling Checklist used by the Registered Pharmacy
  - Revlimid
  - Revlimid Dispense Authorization Form
- Revlimid Treatment Initiation Form
- Revlimid Prescription Authorization Form
- Revlimid *i-SECURE* Patient Brochure
- Revlimid Adverse Event Report
- Revlimid Pregnancy Capture Form

Contact Information:

The National Pharmacovigilance and Drug Safety Centre (NPC)
-Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340
-Toll free phone: 8002490000
-E-mail: npc.drug@sfda.gov.sa
-Website: www.sfda.gov.sa/npc

Salehiya Contact Information:

Ph. Mohammed Waqas
Pharmacovigilance Representative
Salehiya Trading Establishment
E-Mail : m.waqas@salehiya.com
PO Box 991, Riyadh 11421
Kingdom of Saudi Arabia
Tel #+966 1 1464 6955 Ext 362
Fax #+966 1 1463 4362
Mobile #+966 591211197

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i-SECURE
Revlimid® (Lenalidomide) Healthcare Professional Information Pack

Contents

1.0 Introduction

Revlimid belongs to the class of immunomodulatory drugs known as IMiDs® compounds. IMiDs® compounds are structurally related to Thalidomide, i.e. compounds that have been designed using the Thalidomide structural backbone but with chemical modifications to optimize their immunological and anticancer properties.

Revlimid is structurally related to thalidomide, a known human teratogenic substance that causes severe life-threatening birth defects. Revlimid induced, in rats and rabbits, malformations similar to those described with thalidomide.
If Revlimid is taken during pregnancy, a teratogenic effect in humans is expected. Revlimid is therefore contraindicated in pregnant women and in Females of Child Bearing Potential (FCBP) unless they adhere to the conditions of the Revlimid Pregnancy Prevention Program.

The conditions of the Revlimid Pregnancy Prevention Program must be fulfilled for all male and female patients.

2.0 i-SECURE

Revlimid will only be available under a special distribution program, called the i-SECURE program. The aims of this program are to:

- Ensure that use and distribution of Revlimid are closely monitored and well controlled
  a. Only prescribers registered with i-SECURE can prescribe Revlimid
  b. Patients must enroll in the i-SECURE program to receive Revlimid
  c. Only pharmacists/pharmacies registered with i-SECURE can dispense Revlimid

- Ensure that patients taking Revlimid are fully informed about their treatment and – most importantly – that they take all necessary steps to avoid exposing unborn babies to Revlimid
  a. Prescribers must inform patients about the likely benefits and potential risks of Revlimid therapy, and properly explain how potential risks can be avoided or minimized
  b. Patients must formally agree to fully comply with the requirements of the i-SECURE program, by signing a "Revlimid Treatment Initiation Form"
  c. Females of Childbearing Potential (FCBP) are mandated to perform pregnancy tests before taking Revlimid and later on with every single dispense (every 4 weeks), including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation.
  d. Prescribers must provide patients a "Revlimid patient brochure"

For additional copies of this information pack or further information about i-SECURE or Revlimid please contact Biologix/Salehiya Tel #+966 1 1464 6955 Ext 362

3.0 i-SECURE: Responsibilities for registered participants

3.1 Prescribers:

1) All prescribers MUST be registered with i-SECURE to prescribe Revlimid

   a. To register, prescribers must complete a "Revlimid Prescriber Registration Form" after receiving this "Revlimid Healthcare Professional Information Pack"

   b. Complete and sign the "Revlimid Prescriber Registration Form" and provide to Biologix

   c. For further information about the registration process please contact Biologix /Salehiya Tel #+966 1 1464 6955 Ext 362 or contact your local medical representative

2) Prescribers MUST agree to the following:

   a. Provide counseling to each patient:

      - Why it is important not to expose unborn babies to Revlimid and what patients can do to prevent such exposure
      - What i-SECURE registered patients' responsibilities are in this regard
      - Advise all patients on Revlimid not to donate blood
      - Advise all male patients not to donate semen or sperm when taking
      - Revlimid Advise all patients who are or might be engaged in any sexual activity to adhere to the effective contraception methods
      - Advise all FCBP patients not to breast feed if Revlimid therapy was initiated post-partum
      - Advise all patients not to share Revlimid
      - Return unused Revlimid to the pharmacist

- On the likely benefits and possible side effects of Revlimid treatment
    - How to recognize potentially serious side effects
    - How to minimize the risk of developing serious side effects
    - What to do if symptoms of potentially serious side effects develop

b. Prescribe no more than a 4-week (28 day) supply of Revlimid per prescription for females of childbearing potential, or a maximum of 12-week (84-day) supply for all other patients

c. Provide each patient with the "Revlimid Patient Brochure"

d. Enroll each patient by submitting a completed and signed "Revlimid Treatment Initiation Form" for each new patient being prescribed Revlimid. This form must be completed by both the prescriber and the patient. The "Revlimid Treatment Initiation Form" is a written confirmation that the patient has received and understood information on the safe use of Revlimid. This form is to be completed at initiation of treatment for the first time or after there has been a change in the patient's risk category (e.g. Female of childbearing potential changes to female not of childbearing potential)

e. Send the "Revlimid Treatment Initiation Form" e.g. by email, to pharmacovigilance@blgx.net or by fax, to Biologix on + 966 1462 8381

f. Retain a copy of the "Revlimid Treatment Initiation Form" in the patient's file

g. Biologix will then register the patient and forward a "Patient Registration Confirmation Letter" with a "Unique Patient Identification Number" (UPIN) to the prescriber. The UPIN must be written on each new "Revlimid Prescription Authorization Form", which must accompany each prescription for that particular patient. The "Revlimid Prescription Authorization Form" shows:

- Patient was counseled on safe use of Revlimid
- Patient risk category (female of childbearing potential; female NOT of childbearing potential; male)
- Pregnancy test date and result for female of childbearing potential (Prescriptions must be dispensed within a maximum of 7 days after the last negative pregnancy test date)
- Dosing prescribed
- Milligram strength and number of capsules to be dispensed

h. Provide the patient with a completed and signed "Revlimid Prescription Authorization Form" with each Revlimid prescription. The patient must present this form to the pharmacy, along with his prescription, or the prescriber may send the "Revlimid Prescription Authorization Form" with each prescription prescription to the pharmacy

i. Adhere to i-SECURE guidelines when writing a prescription for Revlimid® (Lenalidomide)

3.2 Patients:

a. Patients MUST be enrolled in the i-SECURE program to receive Revlimid

1. Each patient (or his/her parent, legal guardian or authorized representative) must complete and sign the "Revlimid Treatment Initiation Form"
2. Patients must present the "Revlimid Prescription Authorization Form" to the pharmacy, along with their prescription or the prescriber may send the "Revlimid Prescription Authorization Form" and the Revlimid prescription to the pharmacy

b. Patients MUST agree to comply with all requirements of the i-SECURE program

1. Each patient must take all necessary steps to avoid exposing an unborn baby to Revlimid

3.3 Pharmacists:

a. Pharmacies must be registered with i-SECURE in order to dispense Revlimid

1. To register, pharmacies must complete and sign a "Revlimid Pharmacy Registration Form" after receiving this "Revlimid Healthcare Professional Information Pack" and send the completed form to Biologix
2. Biologix will approve dispenses and authorize shipments to the registered pharmacy
3. For further information about the registration process please contact Biologix/Salehiya Tel #+966 1 1464 6955 Ext 362 or your local Biologix medical representative

b. i-SECURE registered pharmacists MUST agree to do the following:

1. Obtain a Revlimid prescription and the "Revlimid Prescription Authorization Form" and check the "Revlimid Prescription Authorization form" for completeness
2. Provide counseling to each patient and fill the "Education and Counseling Check list used by the Registered Pharmacy"
3. Send the signed "Revlimid Prescription Authorization Form" and "Education and Counseling Check list" e.g. by email, to pharmacovigilance@blgx.net or by fax, to Biologix on + 966 1462 8381
4. Dispense to a patient Revlimid as per Biologix approval sent by fax to the pharmacy
5. Dispense no more than a 4-week (28-day) supply of Revlimid for FCBP and up to a maximum of 12-week (84-day) supply for all other patient risk categories provided it was so approved by Biologix
6. A new prescription is required for further dispensing
7. For subsequent prescriptions, verify there are 7 days or less since the last pregnancy test occurred.
8. For subsequent prescriptions, verify there are 7 days or less remaining of the 28-day cycles on the existing prescription
9. Biologix has the right to audit pharmacy's compliance with i-SECURE and check stock present at pharmacy

Warning:

Please be informed that your registration in i-SECURE program can be deactivated once any of i-SECURE requirements are not met.
In case of incompliance, Biologix has the right to cease collaboration regarding controlled Pomalidomide under i-SECURE.

4 What registered prescribers must do before prescribing Revlimid according to patient risk categories

The i-SECURE segments Revlimid patients in different risk categories according to their childbearing potential:

a. Female of childbearing potential

Females who do not meet the below definition of Female NOT of childbearing potential should be classified as FCBP.

b. Female NOT of childbearing potential

1. Females ≥ 50 years old and naturally amenorrhoeic for ≥ 2 years
   - Amenorrhoea following cancer therapy or during breast-feeding does not does not rule out childbearing potential
2. Females that have premature ovarian failure confirmed by a gynecologist
3. Females that have not begun menstruation
4. Females with bilateral salpingo-oophorectomy or hysterectomy
5. Females with XY genotype, Turner's syndrome or uterine agenesis

c. Male

To minimize the risk of a pregnancy occurring under the treatment of Revlimid there are different requirements for each of these patient's risk categories

i-SECURE requirements for females of childbearing potential (FCBP)

1. Pregnancy testing

To confirm absence of a pregnancy, FCBP must have a medically supervised negative pregnancy test with a minimum sensitivity of 50 mIU/ml before starting Lenalidomide.

- A medically supervised pregnancy test should be performed during the consultation, when Revlimid is prescribed, or in the 7 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 that the FCBP patient is not pregnant when she starts treatment with Revlimid
- During 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
- The prescriber documents the date and result of each pregnancy test on the "Revlimid Prescription Authorization Form"

2. Contraception requirements for females of childbearing potential

- MUST be established on effective contraception for at least 4 weeks before initiating Revlimid therapy
- Use simultaneously two reliable methods of contraception simultaneously for 4 weeks before Revlimid therapy, during therapy, during dose interruption and until 4 weeks after therapy

There must be no more than 7 days between the dates of the last negative pregnancy test and the dispensing of Revlimid. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day if not established on effective contraception, the patient should be referred to an appropriately trained Healthcare Professional for contraceptive advice before initiating Revlimid treatment.

3. Examples of effective methods of contraception

a. Highly effective methods

- Intra Uterine Device (IUD)
- Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills e.g. desogestrel)
- Tubal ligation
- Partner's vasectomy

b. Effective methods

- Male condom
- Diaphragm
- Cervical cap

Contraceptive methods must include: At least 1 highly effective method AND 1 additional effective barrier method used at the same time.

Hormonal contraception should be initiated 4 weeks before starting Revlimid treatment.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking Revlimid and dexamethasone, combined oral contraceptive pills are not recommended.

Advise patient that if a pregnancy does occur whilst she is receiving Revlimid, she must stop treatment immediately and inform her doctor immediately.

4. In the event of pregnancy whilst on treatment with Revlimid

- Stop treatment with Revlimid
- Refer the patient to a Gynecologist/Obstetrician experienced in reproductive toxicity
- Complete the "Revlimid Pregnancy Capture Form" and send it immediately to Biologix and/or Celgene at the numbers/Addresses stated in the "Revlimid Pregnancy Capture Form"
- Notify immediately Biologix at +966-11-2038222 Exts: 2340-2334-2354-2353-2356-2317 or Salehiya at: Ph. Mohammed Waqas-Pharmacovigilance Representative-Salehiya Trading Establishment - E-Mail : m.waqas@salehiya.com - PO Box 991, Riyadh 11421 - Kingdom of Saudi Arabia - Tel #+966 1 1464 6955 Ext 362 Fax #+966 1 1463 4362 Mobile #+966 591211197

Biologix will wish to follow-up about the progress of all pregnancies occurring under Revlimid treatment

Revlimid® (Lenalidomide)

i-SECURE requirements for females not of childbearing potential

- Provide counseling as described in section 3.1.2
- Treating Physicians are advised to refer their patient for a gynecological opinion if at all unsure as to whether a woman meets the criteria for being of a female NOT of childbearing potential

i-SECURE requirements for males

Traces of Revlimid are present in semen, therefore:

- Male patients should practice complete abstinence or use condoms during sexual intercourse with a pregnant female or a female of childbearing potential throughout the duration of treatment, during dose interruption and for 4 weeks after cessation of treatment if their partner is not established on suitable contraception (even if the male patient has undergone vasectomy)
- Male patients must not donate semen or sperm during therapy including dose interruptions and for 4 weeks following the discontinuation of Revlimid

Male patients should be instructed that if their partner becomes pregnant whilst they take Revlimid or shortly after the patient stopped Revlimid treatment, he should inform his doctor immediately. Inform your patient which are the effective contraceptive methods that his female partner can use.

5.0 Writing subsequent Revlimid prescriptions

When a patient requires a new prescription, simply record the UPIN on the "Revlimid Prescription Authorization Form" which should accompany the Revlimid prescription and forward it to Biologix

6.0 Reporting of Adverse Events

The safe use of Revlimid is of paramount importance. As part of the ongoing safety monitoring, Biologix wish to learn of Adverse Events that have occurred during the use of Revlimid.

Biologix reports adverse events to Celgene Global Drug Safety & Risk Management in accordance to the Pharmacovigilance Agreement.

For reporting an Adverse Event or a pregnancy, please contact Biologix/ Salehiya Establishment at +966-11-2038222 Exts: 2340-2334-2354-2353-2356-2317 or fill in the "i-SECURE Adverse Event Report Form

7.0 For ADR reporting

Salehiya:
Ph. Mohammed Waqas
Pharmacovigilance Representative
Salehiya Trading Establishment
E-Mail : m.waqas@salehiya.com
PO Box 991, Riyadh 11421
Kingdom of Saudi Arabia
Tel #+966 1 1464 6955 Ext 362
Fax #+966 1 1463 4362
Mobile #+966 5912111

The National Pharmacovigilance and Drug Safety Centre (NPC)
-Fax: +966-11-205-7662
-Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340
-Toll free phone: 8002490000
-E-mail: npc.drug@sfda.gov.sa
-Website: www.sfda.gov.sa/npc

8.0 i-SECURE Patient Brochure

Please refer to the "Revlimid Patient Brochure" included in the end of this folder

i-SECURE

Prescriber Registration Form

Revlimid® (Lenalidomide)

This form will need to be completed by physicians to register into the i-SECURE program before Prescribing Revlimid®. This is a one time registration.

Please fill out in capital letters

Prescriber Details

First Name:		
Last Name:		
Specialty:		
Practitioner Registration/License Number:		
Hospital Name and Address:		
E-mail Address:		
Telephone:		Fax:

I have read and understood the i-SECURE Healthcare Professional Information Pack, explaining the risks for patients receiving Revlimid®, particularly the risk of fetal exposure, and I shall comply with the requirements of the i-SECURE program.

Signature _____ Date: | | | | | | | | |

D D M M Y Y Y Y

Please provide to Biologix/ Salehiya Establishment before prescribing Revlimid®

Salehiya Contact Information:

Ph. Mohammed Waqas
Pharmacovigilance Representative
Salehiya Trading Establishment
E-Mail : m.waqas@salehiya.com
PO Box 991, Riyadh 11421
Kingdom of Saudi Arabia
Tel #+966 1 1464 6955 Ext 362
Fax #+966 1 1463 4362
Mobile #+966 591211197

i-SECURE

Pharmacy Registration Form

Revlimid® (Lenalidomide)

This form will need to be completed by pharmacist to register into the Revlimid® Risk Management Program before dispensing Revlimid® to patients. This is a one time registration.
Please fill out in capital letters

Pharmacist Details (Head Pharmacist)

First Name:		
Last Name:		
Dispensing License Number:		
Pharmacy Address:		
Telephone:		Fax*:
E-mail Address:		
*The fax number will be used by Biologix/ Salehiya Establishment to authorize Revlimid prescriptions		

I have read and understood the Revlimid® i-SECURE Healthcare Professional Information Pack explaining the risks for patients receiving Revlimid, particularly the risk of fetal exposure.
I agree to implement the following i-SECURE risk minimization procedures when dealing with prescriptions for Revlimid®:

1.	All pharmacists dispensing Revlimid will have read and understood the i-SECURE Healthcare Professional Information Pack.
2.	Revlimid will be dispensed only if: - The prescription is accompanied by a completed Revlimid® Prescription Authorization Form AND - After receiving authorization from Biologix AND - Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription - Will dispense no more than a 4-week (28 day) supply of Revlimid per prescription to women of childbearing potential, or a 12-week (84-day) supply for all other categories provided it was so approved by Biologix
3.	Compliance with these procedures will be subject to audits by Biologix

Warning:

Please be informed that your registration in i-SECURE program can be deactivated once any of i-SECURE requirements are not met.
In case of incompliance, Biologix has the right to cease collaboration regarding Revlimid® under i-SECURE.

Signature _____ Date: | | | | | | | | |

D D M M Y Y Y Y

Please provide this form to Biologix/ Salehiya Establishment before dispensing Revlimid® to Patients.
A copy must be filed at the pharmacy

i-SECURE

طلب المباشرة بالعلاج

Revlimid®(Lenalidomide)

يجب ملء هذا الطلب لكل مريض قبل المباشرة بعلاج Revlimid® (Lenalidomide) وفي حال تغيير في وضع المريض. يُرجى الاحتفاظ بنسخة عن هذا الطلب في ملفّ المريض الطبي. يهدف هذا الطلب إلى حماية المريض، او الجنين في حال الحمل، من خلال إطلاع المريض بشكل كامل على الاستخدام الآمن ل Revlimid® (Lenalidomide).

يُرجى ملء الطلب بخط واضح

من خلال طلب المباشرة بالعلاج هذا:

– يؤكد الطبيب المعالج أنّه سيشرح شخصيّاً للمريض الموقِّع سبل الوقاية عند تناول Revlimid® (Lenalidomide).

– يؤكد المريض أنّه سيمتثل تماماً لشروط برنامج i-SECURE Revlimid® (Lenalidomide) كافةً.

المعلومات عن المريض:

الاسم الثلاثي:			
تاريخ الولادة: (اليوم/الشهر/السنة)	_____ _____ _____		
تاريخ الاستشارة: (اليوم/الشهر/السنة)	_____ _____ _____		
المدينة:		رقم الهاتف:	

سيتلقّى المريض علاجاً بـ Revlimid® (Lenalidomide) لمعالجة:

☐ المايلوما المتعدّدة (Multiple Myeloma)

☐ حالات أخرى (يُرجى التحديد)

_____

وضع المريض:

☐ امرأة قادرة على الانجاب (امرأة دون الخمسين من عمرها، لم تبلغ سن اليأس بشكل طبيعي لمدّة عامَين. لم تخضع لعمليّة استئصال الرحم)

☐ امرأة غير قادرة على الانجاب

☐ رجل

الطبيب

لقد شرحت بشكل كاف إلى المريض الوارد اسمه أعلاه طبيعة العلاج بواسطة Revlimid® (Lenalidomide)، وهدفه، ومخاطره، لا سيّما طرق الوقاية الخاصة المطلوبة لعدم تعريض أي جنين لمفاعيل Revlimid® (Lenalidomide) وفق برنامج i-SECURE Revlimid® (Lenalidomide).

تمّ تأمين المستندات التالية إلى المريض (يُرجى وضع إشارة اذا اعطي للمريض):

☐ كتيّب المريض حول برنامج i-SECURE Revlimid® (Lenalidomide)

إسم الطبيب الثلاثي _____

المستشفى / المركز _____

توقيع الطبيب _____ التاريخ (اليوم/الشهر/السنة) _____

i-SECURE

طلب المباشرة بالعلاج

Revlimid®(Lenalidomide)

المريض

أؤكّد أنّني حصلت على المعلومات حول المنافع والآثار الجانبيّة الضارة المحتملة لعلاج Revlimid® (Lenalidomide)، بما في ذلك أهميّة عدم تعريض أي جنين ل Revlimid® (Lenalidomide)، وما يُمكنني فعله لتجنّب تعريض الجنين للدواء.

إنّني أسمح بموجبه ل بيولوجيكس في الحصول على المعلومات الطبية الخاصة بي لأهداف خطة إدارة المخاطر.

كما أؤيّد أنّني فهمتُ وأنّني أمتثل لشروط برنامج i-SECURE، وأوافق على أن يباشر طبيبي بوصف علاج Revlimid® (Lenalidomide)، لي.

اسم المريض _____

التوقيع _____ التاريخ (اليوم/الشهر/السنة) _____

يُرجى إرسال هذا الطلب عبر الفاكس إلى بايولوجيكس/صالحية على الرقم السعودية 8381 1462 966 + or Riyadh at
Jeddah/Damman at +966 3826 0017

عند الحصول على هذا الطلب، تبدأ بايولوجيكس بتسجيل المريض وتُرسل إلى الطبيب رقم تعريفي فريد لكل مريض (UPIN).
يجب تدوين ال UPIN على كل طلب إذن جديد بوصف Revlimid® (Lenalidomide)، الذي يجب أن يُرافق كل وصفة لهذا المريض.

i-SECURE

Treatment Initiation Form

Revlimid® (lenalidomide)

This form must be completed for each patient prior to the initiation of their Revlimid® (lenalidomide) treatment and in the case of a change in the patient's risk category. Retain a copy of this form with their medical records. The aim of the "Treatment Initiation Form" is to protect patients and any possible unborn children by ensuring that patients are fully informed on the safe use of Revlimid® (lenalidomide).

Please fill the two pages in capital letters

With this Treatment Initiation Form:
- The prescribing physician confirms individual counseling for the signing patient receiving Revlimid® (lenalidomide)
- The patient confirms to fully comply with all requirements of the Revlimid® (lenalidomide) *i-SECURE* program

Patient Details

Name: (First Name, Middle Name, Family Name)			
Date of birth	____ DD ____ MM ____ YYYY		
Counseling Date	____ DD ____ MM ____ YYYY		
City:		Phone Number:	

Patient will receive Revlimid® (lenalidomide) to treat

☐ Multiple Myeloma

☐ Other (please specify):.....

.....

Status of Patient

☐ Female of Childbearing Potential
(Females < 50, not naturally post menopausal for 2 years and have not had a hysterectomy)

☐ Female of Non-Childbearing Potential

☐ Male

Prescriber

I have fully explained to the patient named above, the nature, purpose and risks of the treatment associated with Revlimid® (lenalidomide), particularly the special precautions required to prevent the exposure of an unborn child to Revlimid® (lenalidomide) in accordance to the Revlimid® (lenalidomide) *i-SECURE* Program.

The following material has been provided to the patient (please tick box):

☐ *i-SECURE* Patient Brochure

Prescriber Name: _____
(First/Middle/Family Names)

Hospital / Centre _____

Prescriber Signature _____ Date (DD/MM/YYYY) _____

i-SECURE

Treatment Initiation Form

Revlimid® (Lenalidomide)

Patient

I confirm that I have received information on the likely benefits and possible side effects of Revlimid® (lenalidomide) treatment, including why it is important not to expose unborn babies to Revlimid® (lenalidomide) and what I can do to prevent such exposure.

I further confirm that I understand and will comply with the requirements of the *i-SECURE* Program, and I agree that my doctor can initiate my treatment with Revlimid® (lenalidomide)

Patient's Name: _____

Signature _____ Date (DD/MM/YYYY) _____

Please fax this form to Biologix/ Salehiya Establishment at + 966 1462 8381 or Jeddah/Damman at +966 3826 0017. Upon receipt of this form, Biologix will register the patient and forward to the prescriber a Unique Patient Identifier Number (UPIN). The UPIN must be written on each new Revlimid® (lenalidomide) Prescription Authorization Form, which must accompany each prescription for this patient.

RMP-REV-TIFe-KSA-V.2.1-DEC15

i-SECURE

Patient Registration Confirmation Letter

Revlimid® (lenalidomide)

To:	
Date:	

Biologix/ Salehiya Establishment hereby confirm registration of the patient _____ in thei-SECURE Risk Management Program

Mr/Ms_____has been given UPIN _____

Salehiya Contact Information:

Ph. Mohammed Waqas
Pharmacovigilance Representative
Salehiya Trading Establishment
E-Mail : m.waqas@salehiya.com
PO Box 991, Riyadh 11421
Kingdom of Saudi Arabia
Tel #+966 1 1464 6955 Ext 362
Fax #+966 1 1463 4362
Mobile #+966 591211197

i-SECURE

Prescription Authorization Form

Revlimid® (Lenalidomide)

A newly completed copy of this form MUST accompany every Revlimid® prescription. Completion of this form is mandatory for ALL patients.

Please fill the two pages in capital letters

Patient Details

First Name:	
Last Name:	
Unique Patient Identification Number:	
Date of birth:	_____ _____ _____ DD MM YYYY
Dose prescribed:	_____mg/day_____days

Patient Risk Category (tick one), and answer accordingly

☐ Female of non-childbearing potential		
☐ Male		
	The patient has been counseled about the teratogenic potential of treatment with Revlimid® and understands the need to use a condom if involved in sexual activity with a woman of childbearing potential who is not using an effective method of pregnancy prevention?	Yes ☐ No ☐
☐ Female of childbearing potential		
	The patient has been counseled about the teratogenic potential of treatment with Revlimid®, the need to avoid pregnancy and has been using an effective method of pregnancy prevention for at least 4 weeks?	Yes ☐ No ☐
	Last pregnancy test date (DD/MM/YYYY)	
	Last pregnancy test result negative?	Yes ☐ No ☐

i-SECURE

Prescription Authorization Form

Revlimid® (lenalidomide)

Prescriber

I have read and understood the Revlimid® i-SECURE Healthcare Professional Information Pack, and confirm that the patient has signed a Revlimid® Treatment Initiation Form.

Prescriber Name _____

Prescriber Signature _____ Date (DD/MM/YYYY) _____

Patient

I agree that by signing this prescription, I know and understand all potential risks that may happen due to taking Revlimid® including the potential birth defects or death to unborn babies when exposed to Revlimid®.

I further confirm that I will comply with the requirements of the i-SECURE program regarding the use of Revlimid®.

Patient Name _____

Signature _____

Pharmacy Confirmation

Note to pharmacist: the date of the prescription must match the date on this Revlimid® Prescription Authorization Form. Do not dispense to FCBP unless the pregnancy test is negative and was performed within 7 days of the prescription date.

I am satisfied that the "Revlimid® Prescription Authorization Form" has been completed fully and that I have read and understood the i-SECURE Healthcare Professional Information Pack

Strength: _____ Duration: _____

Quantity of capsules to be dispensed: _____

Pharmacist Name: _____

Pharmacy Name: _____

Signature _____ Date (DD/MM/YYYY) _____

Please fax this form to Biologix/ Salehiya Establishment at + 966 1462 8381
Upon receipt of this form Biologix will advise the pharmacy on approval of Revlimid® dispense.

RMP-REV-PAF-KSA-V.2.1-DEC15

i-SECURE

Education and Counseling Checklist Used by the Registered Pharmacy

Revlimid® (lenalidomide)

The following checklist must be completed by an i-SECURE registered pharmacy. Please use the checklist that applies to the patient risk category written on the Prescription Authorisation Form.

Checklist for Females of Childbearing Potential

I counseled patients on:

- ☐ Potential fetal harm
- ☐ Using 2 forms of effective birth control at the same time or abstaining from heterosexual sexual intercourse
- ☐ Continuation of 2 forms of birth control if therapy is interrupted and for 4 weeks after therapy is discontinued
- ☐ Obtain a pregnancy test repeated every 4 weeks in females with regular menstrual cycles.
- ☐ The need to stop taking Revlimid® (lenalidomide) right away in the event of becoming pregnant and to call their healthcare provider immediately. Female partners of males taking Revlimid® (lenalidomide) must call their healthcare provider right away if they get pregnant
- ☐ Possible side effects due to neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism
- ☐ Reminder 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 Revlimid® (lenalidomide)
- ☐ Not sharing medication
- ☐ Not donating blood while taking Revlimid® (lenalidomide) and for 4 weeks after stopping Revlimid® (lenalidomide)
- ☐ Not to break, chew, or open Revlimid® (lenalidomide) capsules
- ☐ Instructions on Revlimid® (lenalidomide) dose and administration: Dose _____ # of Capsules Dispensed _____

Checklist for Females NOT of Childbearing Potential

I counseled patients on:

- ☐ Possible side effects due to neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism
- ☐ Reminder 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 Revlimid® (lenalidomide)
- ☐ Not sharing medication
- ☐ Not donating blood while taking Revlimid® and for 4 weeks after stopping Revlimid® (lenalidomide)
- ☐ Not to break, chew, or open Revlimid® (lenalidomide) capsules
- ☐ Instructions on Revlimid® (lenalidomide) dose and administration: Dose _____ # of Capsules Dispensed _____

Checklist for Males

I counseled patients on:

- ☐ Potential fetal harm and contraception (wearing a latex condom when engaging in sexual intercourse with a female of childbearing potential)
- ☐ Possible side effects due to neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolism
- ☐ Reminder 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 Revlimid® (lenalidomide)
- ☐ Not sharing medication
- ☐ Not donating blood while taking Revlimid® (lenalidomide) and for 4 weeks after stopping Revlimid® (lenalidomide)
- ☐ Not to break, chew, or open Revlimid® (lenalidomide) capsules
- ☐ Instructions on Revlimid® (lenalidomide) dose and administration: Dose _____ # of Capsules Dispensed _____

DO NOT dispense or ship Revlimid® (lenalidomide) to a patient unless all the following are done:

- ☐ You have counseled the patient
- ☐ You have obtained a dispense authorization from Biologix
- ☐ The i-SECURE patient brochure is provided to the patient
- ☐ You confirm that current prescription is 7 days or less remaining on a previous Revlimid® (lenalidomide) prescription

Please fax this form to Biologix / Salehiya Establishment at +966 14628381

i-SECURE

Dispense Authorization Form

Revlimid® (Lenalidomide)

Biologix/ Salehiya Establishment hereby approve the release of Revlimid® capsules to:

Patient Name: .....

UPIN: .....

Prescribed dose: ..... mg/day

Duration: ..... days

Quantity of capsules to be dispensed: ..... caps

Box(es): ..... box(es) Signature: .....

Pharmacy name: .....

Date: .....

i-SECURE

Revlimid®(Lenalidomide) Patient Brochure

Content

Introducing i-SECURE

Your Doctor intends to prescribe Revlimid® for you.

Revlimid® (the trade name for lenalidomide) is a structural analogue to Thalidomide. Thalidomide is a known teratogen that causes severe life-threatening human birth defects. If Revlimid is taken during pregnancy it may cause birth defects or death to an unborn baby.

To avoid fetal exposure, Revlimid® is available only under a special distribution program called i-SECURE.

The i-SECURE program is designed to ensure that Revlimid® therapy is always prescribed and taken in the recommended way.

Key features of the program:

- Only physicians registered with i-SECURE can prescribe Revlimid®
- Only pharmacists/pharmacies registered with i-SECURE can dispense Revlimid®
- Only patients who have been formally enrolled in the i-SECURE program can receive Revlimid®

To enroll, patients must sign a "Revlimid® Treatment Initiation Form" and agree to fully comply with all requirements of the i-SECURE program.

IMPORTANT TO REMEMBER:

Revlimid® may cause birth defects or death to unborn babies.

Special i-SECURE Requirements for Females who are Able to Become Pregnant

Include:

- Females younger than 50 years
- Females that are not naturally postmenopausal for at least two years
- Females that have not had a hysterectomy

Important: do NOT become pregnant:

- During the four weeks before starting Revlimid® treatment
- While taking Revlimid®
- During any interruption in Revlimid® treatment
- During the four-week period following the conclusion of your Revlimid® treatment

Before starting treatment:

1. You must sign a "Revlimid® Treatment Initiation Form", agreeing not to become pregnant while taking Revlimid® and following all requirements within i-SECURE
2. You must use two reliable methods of birth control (contraception) at the same time 4 weeks before starting Revlimid® treatment. Refer below for examples of suitable methods of contraception:
   - Highly effective methods
     - Intra Uterine Device (IUD)
     - Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills e.g. desogestrel)
     - Tubal ligation
     - Partner's vasectomy

o Effective methods

- Male condom
- Diaphragm
- Cervical cap

Contraceptive methods must include: At least 1 highly effective method AND 1 additional effective barrier method used at the same time.

3. You must have a medically supervised pregnancy test done during your consultation with the doctor, when Revlimid® is prescribed, or in the 3 days prior to the visit to the doctor once you had been using effective contraception for at least 4 weeks. The test should ensure that you are not pregnant when you start treatment with Revlimid®
4. You must agree to not breastfeed or donate blood
5. You must agree to never share your Revlimid® capsules
6. You must agree to return unused Revlimid® capsules to your pharmacist

During treatment and dose interruptions:

1. You must continue to use two reliable methods of birth control (contraception) at the same time during treatment and during any interruption in Revlimid® treatment
2. You must also undergo regular medically supervised pregnancy tests every four weeks during treatment
3. You must not breastfeed or donate blood
4. Never share your Revlimid® capsules

Note: If you miss a period, experience any abnormality in menstrual bleeding, become pregnant or have sexual intercourse without using an effective means of birth control (contraception):

- Stop Revlimid® immediately
- Tell your doctor
- Have a pregnancy test

For four weeks after treatment:

1. You must continue to use two reliable methods of birth control (contraception) at the same time
2. You must not breastfeed or donate blood
3. Never share your Revlimid® capsules
4. Return unused Revlimid® capsules to your pharmacist
5. You must undergo a medically supervised pregnancy test 4 weeks after discontinuation of Revlimid® therapy

Note: If you miss a period, experience any abnormality in menstrual bleeding, become pregnant or have sexual intercourse without using an effective means of birth control (contraception):

- Tell your doctor
- Have a pregnancy test

i-SECURE Requirements for Females who are NOT Able to Become Pregnant

Include:

Females who do not meet the below definition of Female NOT of childbearing potential should be classified as Females of childbearing potential (FCBP).

- Females ≥ 50 years old and naturally amenorrheic for ≥ 2 years
  - Amenorrhea following cancer therapy does not rule out childbearing potential
- Females that have premature ovarian failure confirmed by a gynecologist
- Females with bilateral salpingo-oophorectomy or hysterectomy
- Females with XY genotype, Turner's syndrome or uterine agenesis

Before starting treatment:

1. You must sign a "Revlimid® Treatment Initiation Form", indicating that you are not pregnant and do not have the ability to have children and will follow all requirements within i-SECURE
2. You must agree to not donate blood
3. You must agree to never share your Revlimid® capsules
4. You must agree to return unused Revlimid® capsules to your pharmacist

During treatment and during dose interruptions:

1. You must not donate blood
2. Never share your Revlimid® capsules

For four weeks after treatment:

1. You must not donate blood
2. Return unused Revlimid® capsules to your pharmacist

i-SECURE Requirements for Male Patients

Before starting treatment:

1. Revlimid® is present in semen. You must sign a "Revlimid® Treatment Initiation Form", agreeing to use a condom EVERY TIME you have sexual intercourse with a woman who either is or can become pregnant (even if you have had a successful vasectomy) and will follow all requirements within i-SECURE including the following:
   - You must agree to not donate blood, sperm or semen
   - You must agree to never share your Revlimid® capsules
   - You must agree to return unused Revlimid® capsules to your pharmacist

During treatment and during dose interruptions:

1 You must use a condom EVERY TIME you have sexual intercourse with a woman who either is or can become pregnant (even if you have had a successful vasectomy)
2. You must tell your doctor if you have sexual intercourse with a woman without using a condom, or if you think for any reason that your partner may be pregnant
3. You must not donate blood, sperm or semen
4. Never share your Revlimid® capsules

For four weeks after treatment:

1. You must continue to use a condom EVERY TIME you have sexual intercourse with a woman who either is or can become pregnant (even if you have had a successful vasectomy)
2. You must tell your doctor if you have sexual intercourse with a woman without using a condom, or if you think for any reason that your partner may be pregnant
3. You must not donate blood, sperm or semen
4. Never share your Revlimid® capsules
5. Return unused Revlimid® capsules to your pharmacist

Special Warnings and Precautions

Low white blood cells (neutropenia) and low platelets (thrombocytopenia).

Revlimid® causes low white blood cells and low platelets in most patients. You may need a blood transfusion or certain medicines if your blood counts drop too low. If you are being treated for del 5q myelodysplastic syndromes (MDS) your blood counts should be checked weekly during the first 8 weeks of treatment with Revlimid®, and at least monthly thereafter. If you are being treated for multiple myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks and then at least monthly thereafter.

A higher chance for blood clots in your veins and lungs.

Call your healthcare provider or get medical help right away if you get any of these signs or symptoms:

a. shortness of breath
b. chest pain
c. arm or leg swelling

Possible side effects of Revlimid®

Revlimid® may cause serious side effects.
Serious skin reactions. Serious skin reactions can happen with Revlimid® and may cause death. Call your healthcare provider right away if you have any skin reaction while taking Revlimid®.

Tumor lysis syndrome. Metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the breakdown 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, heart beat, seizures, and sometimes death.

Common side effects of Revlimid® are:

diarrhea
itching
rash
tiredness

These are not all the possible side effects of Revlimid®. Tell your healthcare provider about any side effect that bothers you or that does not go away

How should you take Revlimid®?

Take Revlimid® exactly as prescribed and follow all the instructions of the i-SECURE program.

Swallow Revlimid® capsules whole with water once a day. Do not break, chew, or open your capsules

Do not open the Revlimid® capsules or handle them any more than needed. If you touch a broken Revlimid® capsule or the medicine in the capsule, wash the area of your body with soap and water

If you miss a dose of Revlimid®, 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

If you take too much Revlimid® or overdose, call your healthcare provider or poison control center right away

Want to Know More?

* For more information about Revlimid® and/or the i-SECURE program:
  - o Speak with your doctor
  - o Call Salehiya at: Ph. Mohammed Waqas - Pharmacovigilance Representative - Salehiya Trading Establishment - E-Mail : m.waqas@salehiya.com - PO Box 991, Riyadh 11421- - Kingdom of Saudi Arabia - Tel #+966 1 1464 6955 Ext 362 Fax #+966 1 1463 4362 - Mobile #+966 591211197

آي سيكيور i-SECURE
Revlimid® (Lenalidomide)

المحتويات

تقديم "آي سيكيور" i-SECURE:

ينوي طبيبك أن يصف لك Revlimid®.
Revlimid® (الاسم التجاري لـ"لينياليدوميد") مُضاهئ كيميائي للثاليدومايد Thalidomide. الثاليدومايد Thalidomide يُسبّب عيوبًا خلقيّة حادة تُهدّد الحياة.
ففي حال تناول Revlimid® في خلال فترة الحمل، قد يولّد ذلك عيوبًا خلقيّة أو يُسبّب وفاة الجنين.
لتفادي تعريض الجنين للخطر، Revlimid® متوفّر فقط ضمن برنامج توزيع خاص يُعرَف بـ"آي سيكيور".
برنامج "آي سيكيور" مُصمَّم لضمان وصف Revlimid® وتناوله بالشكل الموصى به.

مواصفات البرنامج الأساسيّة:
- الأطباء المسجّلون في برنامج "آي سيكيور" فقط يحقّ لهم وصف Revlimid®
- الصيدليّات المسجّلة/الصيادلة المسجّلون في برنامج "آي سيكيور" فقط يحقّ لها/لهم صرف Revlimid®
- المرضى المسجّلون رسميًّا في برنامج "آي سيكيور" يحقّ لهم تناول Revlimid®

للتسجيل في هذا البرنامج، على المرضى توقيع "استمارة المباشرة بعلاج بواسطة Revlimid®" والموافقة على الامتثال بشكل كامل لشروط برنامج "آي سيكيور".

تذكير:
قد يُسبّب Revlimid® عيوبًا خلقيّة أو حالات وفاة لدى الجنين.

شروط برنامج "آي سيكيور" للنساء القادرات على الانجاب من بينهنّ:

- نساء دون الخمسين من عمرهنّ
- نساء لم يبلغن بعد سن اليأس بشكل طبيعيّ لمدّة عامَيْن على الأقل
- نساء لم يخضعن لعمليّة استئصال الرحم

ملاحظة مهمّة: لا تصبحي حاملاً

- في خلال الأسابيع الأربعة قبل بدء Revlimid®
- في خلال تناول Revlimid®
- في خلال أي انقطاع في علاج Revlimid®
- في خلال الأسابيع الأربعة بعد الانتهاء من العلاج بواسطة Revlimid®

قبل البدء بالعلاج:

- عليكِ التوقيع على "استمارة المباشرة بالعلاج بواسطة Revlimid®" والموافقة على تفاديَ الحمل عند تناول Revlimid® واتباع الشروط كافةً المفروضة في إطار برنامج "آي سيكيور".• كما عليكِ استخدام، في الوقت نفسه، وسيلتَيْن موثوقتَيْن لمنع الحمل، وذلك لمدّة أربعة أسابيع قبل البدء بالعلاج بواسطة Revlimid®، أدناه أمثلة عن وسائل منع حمل موثوقة:
- وسائل منع الحمل عالية الفعاليّة:
  - اللولب الرحمي (IUD)
  - الهرمونات (الزرع الهرموني، جهاز رحمي مُطلِق لمادة الليفونورجاسترال (IUS)، حقن مدخرية لميدروكسي بروجستيرون أسيتات، حبوب بروجسترون مثبّطة للإباضة، مثل الديزوجسترال)
  - ربط قنوات الفالوب
  - قطع قناة المني عند الشريك

- وسائل منع الحمل الفعّالة:

- الواقي الذكري
- الحاجز المهبلي
- غطاء عنق الرحم

- عليك الخضوع لاختبار الحمل تحت إشراف طبي عند استشارة الطبيب، عندما يوصَف Revlimid® لك أو في خلال الأيام الثلاثة ما قبل زيارة الطبيب حينما تستخدمين وسيلة منع حمل فعّالة لأربعة أسابيع على الأقل. يجب أن يؤكّد الفحص الطبي أنّك غير حامل عندما تبدأين العلاج بواسطة Revlimid®.
- عليك الموافقة على عدم الرضاعة أو التبرّع بالدم.
- عليك الموافقة على عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.
- عليك الموافقة على إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.

في خلال العلاج ومقاطعة الجرعات:

١. عليك الاستمرار في استخدام، في الوقت نفسه، وسيلتَيْن موثوقتَيْن لمنع الحمل خلال العلاج وعند مقاطعة Revlimid® .
٢. عليك الخضوع لاختبارات الحمل المنتظمة تحت إشراف طبي كل أربعة أسابيع خلال العلاج.
٣. عليك عدم الرضاعة أو التبرّع بالدم.
٤. يجب عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.

ملاحظة: في حال تفويت دورة شهريّة أو اختبار أي اضطراب في دم الطمث أو في حال الحمل أو العلاقة الجنسية من دون استخدام وسيلة منع حمل فعّالة:

- يجب إيقاف Revlimid® على الفور
- يجب تبليغ طبيبك
- يجب الخضوع لاختبار الحمل

لمدّة أربعة أسابيع بعد العلاج:

- عليك الاستمرار في استخدام، في الوقت نفسه، وسيلتَيْن موثوقتَيْن لمنع الحمل.
- عليك عدم الرضاعة أو التبرّع بالدم.

- يجب عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.
- يجب إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.
- عليك الخضوع لاختبار الحمل تحت إشراف طبي ٤ أسابيع بعد ايقاف العلاج بواسطة Revlimid®

ملاحظة: في حال تفويت دورة شهريّة أو اختبار أي اضطراب في دم الطمث أو في حال الحمل أو العلاقة الجنسية من دون استخدام وسيلة منع حمل فعّالة:

- يجب تبليغ طبيبك
- يجب الخضوع لاختبار الحمل

شروط برنامج "آي سيكيور" للنساء غير القادرات على الانجاب من بينهنّ:

- النساء في سن الخمسين وما فوق واللواتي غابت عنهنّ الدورة الشهريّة بشكل طبيعي لمدّة عامَيْن وأكثر
- انقطاع الطمث إثر علاج ضدّ السرطان لا يستبعد منع الحمل
- النساء اللواتي يعانين فشلاً مبيضيًّا مبكرًا يؤكّد عليه طبيب نسائي
- النساء اللواتي خضعن لعمليّة استئصال الرحم أو استئصال المبيضين وقناتي الفالوب
- النساء مع نمط جيني XY، ومتلازمة تورنر، وانعدام وجود الرحم

قبل البدء بالعلاج:

١. عليك التوقيع على "استمارة المباشرة بالعلاج بواسطة Revlimid®"، مع الإشارة إلى أنّك غير حامل وغير قادرة على الانجاب وضمان اتباع الشروط كافةً المفروضة في إطار برنامج "آي سيكيور"٢. عليك الموافقة على عدم التبرّع بالدم.
٣. عليك الموافقة على عدم مشاركة Revlimid® أبدًا مع آخرين.
٤. عليك الموافقة على إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.

في خلال العلاج ومقاطعة الجرعات:
١. عليك عدم التبرّع بالدم.
٢. يجب عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.

لمدّة أربعة أسابيع بعد العلاج:
١. عليك عدم التبرّع بالدم.
٢. يجب إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.

شروط برنامج "آي سيكيور" للرجال

قبل البدء بالعلاج:
- عليك أن تعرف أن Revlimid® يمرّ في السائل المنوي. عليك التوقيع على "استمارة المباشرة بالعلاج بواسطة Revlimid®" والموافقة على استخدام واقٍ ذكري كل مرة تقيم علاقة الجنسية مع امرأة حامل أو قادرة على الانجاب (وحتّى لو كنت قد خضعت لعمليّة قطع قناة المني ناجحة) وعليك اتباع شروط برنامج "آي سيكيور" كافةً، بما في ذلك:
  - الموافقة على عدم التبرّع بالدم أو السائل المنوي.
  - الموافقة على عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.
  - الموافقة على إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.

في خلال العلاج ومقاطعة الجرعات:
١. عليك استخدام واقٍ ذكري عند إقامة علاقة جنسيّة مع امرأة حامل أو قادرة على الانجاب (وحتى لو كنت قد خضعت لعمليّة قطع قناة المني ناجحة).
٢. عليك إطلاع طبيبك في حال إقامة علاقة جنسية مع امرأة من دون استخدام واقٍ ذكري أو في حال تظنّ، لأي سبب كان، أن شريكتك قد تكون حاملاً.
٣. عليك عدم التبرّع بالدم أو السائل المنوي.
٤. يجب عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.

لمدّة أربعة أسابيع بعد العلاج:

١. عليك استخدام واقٍ ذكري عند إقامة علاقة جنسيّة مع امرأة حامل أو قادرة على الإنجاب (وحتى لو كنت قد خضعت لعمليّة قطع قناة المني ناجحة).
٢. عليك إطلاع طبيبك في حال علاقة جنسيّة مع امرأة من دون استخدام واقٍ ذكري أو في حال تظنّ، لأيّ سبب كان، أن شريكتك قد تكون حاملاً.
٣. عليك عدم التبرّع بالدم أو السائل المنوي.
٤. يجب عدم مشاركة حبوب Revlimid® أبدًا مع آخرين.
٥. عليك إعادة حبوب Revlimid® غير المستخدمة إلى الصيدلي.

تحذيرات واحتياطات استثنائية

انخفاض عدد خلايا الدم البيضاء (نقص العدلات) وانخفاض عدد الصفائح الدموية (نقص الصفيحات).

يسبب علاج Revlimid® انخفاضًا في عدد خلايا الدم البيضاء وانخفاضًا في عدد الصفائح الدموية لدى معظم المرضى. فقد تحتاج إلى نقل الدم أو إلى تناول بعض الأدوية إذا انخفض معدّل الدم عندك انخفاضًا حادًا. إذا كنت تتعالج من متلازمة خلل التنسج النقوي (MDS)، يجب أن تجري فحصًا للدم أسبوعيًا خلال الأسابيع الثمانية الأولى من العلاج ب Revlimid®، وبعد ذلك، يجب أن تجري الفحص أقلّه مرّة كل شهر. أمّا إذا كنت تتعالج من الورم النخاعي المتعدد، فيجب أن تجري فحصًا للدم كلّ أسبوعين خلال الأسابي الثانية عشر الأولى وبعد ذلك، يجب أن تجري الفحص أقلّه مرّة كل شهر.

زيادة خطورة التّعرّض لجلطات الدم في الأوردة والرئتين

يجب أن تتّصل بطبيبك أو أن تقوم بطلب المساعدة الطبية فورًا إذا شعرت بأي من العلامات أو العوارض التالية:

أ. ضيق في التنفس
ب. ألم في الصدر
ج. تورّم في الذراع أو الساق

الآثار الجانبية المحتملة لعلاج Revlimid®

قد يُحدث العلاج ب Revlimid® آثارًا جانبية خطيرة.

ردود فعل جلدية خطيرة يمكن أن تحدث ردود فعل جلدية خطيرة نتيجة العلاج ب Revlimid® وقد تؤدّي إلى الوفاة.
فيجب أن تتّصل بطبيبك على الفور إذا حدثت لك أي ردّة فعل جلدية في خلال فترة خضوعك لعلاج Revlimid®.
متلازمة انحلال الورم المضاعفات الأيضية التي يمكن أن تحدث أثناء علاج مرض السرطان، وأحيانًا تحصل بدون علاج. وتنتج هذه المضاعفات بسبب تحطّم مكوّنات الخلايا السرطانية الميتة وقد تشمل ما يلي:
تغييرات في كيمياء الدم، ارتفاع نسبة البوتاسيوم والفوسفور وحمض اليوريك، وانخفاض معدّل الكالسيوم، ممّا يؤدّي بالتالي إلى تغيرات في وظائف الكلى، ونبضات القلب، وحدوث نوبات وقد يسبّب ذلك الوفاة في بعض الأحيان.

الآثار الجانبية الشائعة لعلاج Revlimid® هي:

- الإسهال
- الحكة
- الطفح الجلدي
- التعب

وهذه ليست كافّة الآثار الجانبية المحتملة لعلاج Revlimid®. يجب أن تخبر طبيبك عن أي آثار جانبية تزعجك أو لا تزول مع الوقت.

كيف يجب أن تأخذ Revlimid® ؟

يجب أن تأخذ Revlimid® تمامًا كما وُصف لك ويجب أن تتّبع كافّة تعليمات برنامج iSECURE. يجب ابتلاع أقراص Revlimid® كاملة مع كوب من الماء مرة واحدة في اليوم. لا تكسر الأقراص أو تمضغها أو تفتحها.
لا تفتح أقراص Revlimid® أو تمسكها أكثر من اللازم. فإذا لمست قرصًا مكسورًا من Revlimid® أو لمست الدواء في داخله، اغسل المنطقة في جسمك التي لمست الدواء بالصابون والماء. إذا فوّتت جرعة من Revlimid®، وقد مرّ أقلّ من اثني عشرة ساعة على الموعد المنتظم، بإمكانك تناولها حالما تذكرت.
أمّا إذا كان قد مرّ أكثر من اثني عشرة ساعة، فتجاوز الجرعة المنسية. لا تأخذ جرعتين في الوقت نفسه. إذا أخذت الكثير من Revlimid® أو جرعة زائدة منه، اتصل على الفور بطبيبك أو بمركز مراقبة السّموم.

هل ترغب في معرفة المزيد من المعلومات؟

لمزيد من المعلومات حول الـRevlimid®‏ و/أو برنامج iSECURE:

- تحدث مع طبيبك

Call Salehiya at: Ph. Mohammed Waqas- Salehiya Trading Establishment -
E-Mail :m.waqas@salehiya.com - Tel #+966 1 1464 6955 Ext 362

اتصل بالمركز الوطني للتيقظ والسلامة الدوائية (NPC)
- الفاكس: 7662-205-11-966+
اتصل بالمركز على الرقم التالي: 2038222–11–966+
واطلب 2340-2334-2354-2353-2356-2317
- الرقم المجاني: 8002490000
- البريد الالكتروني: npc.drug@sfda.gov.sa
- الموقع الالكتروني: www.sfda.gov.sa/npc

Revlimid ®(Lenalidomide) Summary of Product Characteristics

MEDICINAL PRODUCT INFORMATION

WARNING:

EMBRYO-FETAL TOXICITY,

- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of Contraception.

HEMATOLOGIC TOXICITY.

REVLIMID can cause significant neutropenia and thrombocytopenia.

For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.

VENOUS THROMBOEMBOLISM

Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone

REVLIMID

COMPOSITION

Active substance: Lenalidomide.

Excipients: Colourant: E132 (only for 10 mg and 15 mg hard capsules), excipient per capsule.

PHARMACEUTICAL FORM AND AMOUNT OF ACTIVE SUBSTANCE PER UNIT

5 mg, 10 mg, 15 mg and 25 mg hard capsules.

INDICATIONS / POSSIBLE USES

Revlimid is indicated in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one previous drug treatment.

Revlimid is indicated for the treatment of patients with anaemia requiring transfusions resulting from myelodysplastic syndrome with low or intermediate risk 1 associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

DOSAGE/ADMINISTRATION

The treatment must be initiated and monitored by an experienced haematologist or oncologist.

Multiple myeloma
The recommended starting dose is 25 mg Revlimid orally once a day on days 1–21 of the repeating 28-day treatment cycles. The recommended dose of dexamethasone is 40 mg orally once a day on days 1–4, 9–12 and 17–20 of each 28-day cycle during the first 4 treatment cycles and then 40 mg once daily on days 1–4 of each cycle. Treatment should be continued until disease progression or until the occurrence of unacceptable toxicity.

Dose adjustment
Recommended dose adjustments during multiple myeloma treatment and restart of treatment
Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

• *Dose reduction steps*

Starting dose	25 mg
Dose level 1	15 mg

Dose level 2	10 mg
Dose level 3	5 mg

Platelet counts

Thrombocytopenia When platelets	Recommended Course
First fall to < 30 x 109/l	Interrupt lenalidomide treatment
Return to ≥ 30 x 109/l	Resume lenalidomide at Dose Level 1
For each subsequent drop below 30 x 109/l	Interrupt lenalidomide treatment
Return to ≥ 30 x 109/l	Resume lenalidomide at next lower dose level (Dose Level 2 or 3) once daily. Do not dose below 5 mg once daily.

Absolute Neutrophil counts (ANC)

Neutropenia When neutrophils	Recommended Course
First fall to < 0.5 x 109/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 109/l when neutropenia is the only observed toxicity	Resume lenalidomide at Starting Dose once daily
Return to ≥ 0.5 x 109/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 109/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 109/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 syndrome

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (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. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment

Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- *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

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/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)

<u>Dose adjustment for other reasons</u>

If a non-scaly grade 3 rash (with blistering), grade 3 neuropathy or grade 2 allergic reaction occurs, the treatment must be suspended. It can be resumed at the next dose down after appropriate regression to ≤ grade 1.

If a scaly rash (with blistering), a grade 4 non-scaly rash (with blistering), grade 4 neuropathy or ≥ grade 3 allergic reaction occurs, Revlimid must be stopped.

If constipation (≥ grade 3) occurs, the treatment must be suspended and treatment of the constipation initiated. The treatment with Revlimid can be resumed at the next dose down after regression of the constipation to ≤ grade 2.

If a venous thrombosis/embolism (≥ grade 3) occurs, the treatment must be suspended and anticoagulant treatment initiated. Resumption of the therapy is at the physician's discretion (keeping the same dose).

Other grade 3/4 toxicities

For other grade 3/4 toxicities judged to be related to Revlimid, the treatment should be stopped and restarted at the next dose down at the physician's discretion once the toxicity has resolved to ≤ grade 2.

Method of Administration

Revlimid capsules should be taken at the same time each day, with or without meals, but with water. The capsules should not be opened or chewed. Hands should be washed immediately after contact with the capsules. Care must be taken to ensure that the powder contained in the capsules is not inhaled and does not come into contact with the skin or mucous membranes (e.g. in the case of damage to a capsule). If skin contact occurs, the site should be washed with soap and water. If the product comes into contact with the eyes, they should be rinsed with water.

If less than 12 hours have elapsed since a dose of Revlimid has been missed, the dose can be taken. 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. Do not take 2 doses at the same time.

Special dosage instructions

Paediatric patients:

Safety and effectiveness in paediatric patients below the age of 18 have not been established. For that reason, Revlimid should not be used in this age group.

Elderly Patients:

Dose adjustments are not necessary. Since elderly patients are more likely to have reduced renal function, renal function should be monitored on a regular basis in these patients

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age. REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney, therefore 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. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

- *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 daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[3] The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment.

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

- *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)

Patients with liver function disorders:

Revlimid has not been investigated in patients with disorders of liver function and there are no special dosage recommendations.

Cessation of treatment because of insufficient efficacy in MDS patients

If at least a slight response, i.e. at least a 50% improvement is not seen 16 weeks after the start of the Revlimid treatment, cessation of treatment due to lack of efficacy is recommended.

CONTRAINDICATIONS

Pregnancy

Women of childbearing potential except when all of the conditions of the i-SECURE (Pregnancy Prevention Programme) have been fulfilled (see "Warnings and Precautions").

Hypersensitivity to lenalidomide or any of the excipients.

WARNINGS AND PRECAUTIONS

Pregnancy Prevention Programme

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.

Counselling

Lenalidomide is contraindicated in women of childbearing potential unless all of the following conditions are met:

- the patient understands the expected teratogenic risk to the unborn child.
- she understands the need for using two forms of effective contraception without interruption for 4 weeks prior to the start of treatment, throughout the entire treatment including interruptions to treatment, and for 4 weeks after the end of treatment.
- even if a female patient of childbearing potential is amenorrhoeic, she must follow all of the recommendations for effective contraception.
- she should be capable of adhering to effective contraceptive measures.
- She is informed and understands the consequences of a pregnancy and the necessity of seeking medical advice promptly if a pregnancy is suspected.
- She understands the need for pregnancy tests every 4 weeks (unless confirmed tubal sterilization) and is willing to have them done.
- She has confirmed that she understands the risks and the necessary safety precautions associated with taking lenalidomide.

The prescribing physician must ensure in women of childbearing potential that

- the patient fulfils the above conditions.
- the patient complies with the conditions for contraception, including confirmation of an adequate level of understanding.
- the patient has used two forms of effective contraceptive measures for at least 4 weeks before the start of treatment and will continue to use two forms of effective contraceptive measures for the entire treatment period, including treatment interruptions, and for at least 4 weeks after completing treatment. - there is a negative result of a pregnancy test prior to the start of treatment.

Contraception

Women of childbearing potential must use two forms of effective contraceptive methods for 4 weeks before the start of treatment, throughout treatment, including treatment interruptions, and for 4 weeks after completing treatment. If effective contraceptive methods have not been used previously, the patient must be referred to a medical counselling service, where she will receive comprehensive counselling regarding effective contraceptive methods.
The following can be regarded as effective contraceptive methods:

- Highly effective methods:
  - Intra Uterine Device (IUD)
  - Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills e.g. desogesterol)
  - Tubal ligation
- Partner's vasectomy

- Effective methods:
  - Male condom
  - Diaphragm
  - Cervical cap

Because of the increased risk of venous thromboembolism on lenalidomide, combined oral contraceptives are not recommended. If a patient is already using combined oral contraceptives, a change to another contraceptive method should be considered. The risk of venous thromboembolism persists for 4-6 weeks after cessation of treatment with combined oral contraceptives. If other methods cannot be used, thrombosis prophylaxis should be considered during the continued use of combined oral contraceptives. The patient should be properly informed about the risk of venous thromboembolism.

Intrauterine devices have an increased risk of infections during insertion and can lead to irregular vaginal bleeding. Therefore these methods are not recommended.

Pregnancy tests
Pregnancy tests with a sensitivity of at least 50 mIU/ml hCG must be performed in women of childbearing potential.

Any case of a patient with a positive pregnancy test must be reported immediately as per the requirements of the Pregnancy Prevention Program.

- *Before the start of treatment*

A pregnancy test must be performed during the consultation at which lenalidomide is prescribed, or within seven days prior to the appointment with the prescribing physician, after the patient has used effective contraception for at least 4 weeks. The test is intended to ensure that the patient is not pregnant before starting treatment with lenalidomide.

- *During and after completing treatment*

A pregnancy test must be repeated every 4 weeks (unless confirmed tubal sterilization), including 4 weeks after the end of treatment. These pregnancy tests should be done during the consultations at which lenalidomide is prescribed, or within seven days before the consultation.

Pregnancy tests, the prescribing and dispensing of lenalidomide should ideally occur on the same day. Lenalidomide must be dispensed within a maximum of 7 days after the last pregnancy test.

Programme for male patients

For male patients taking Revlimid, clinical data have demonstrated the presence of this active substance in the semen. Therefore, male patients with partners of childbearing potential not established on suitable contraception should use condoms during sexual intercourse during the duration of treatment with Revlimid, during dose interruption and for at least 4 weeks after the end of the treatment (even if the male patient has undergone a vasectomy). Men who take Revlimid must fulfil the following conditions:

- They must understand the expected teratogenic risk if they are having sexual intercourse with a woman of childbearing potential.
- They must understand and agree to use a condom when they have sexual intercourse with a woman of childbearing potential for the entire duration of treatment, including treatment interruptions, and for at least 4 weeks after the end of treatment treatment (even if the male patient has undergone a vasectomy).

The prescribing physician must ensure that male patients understand the need to use a condom when they have sexual intercourse with a woman

of childbearing potential for the entire duration of treatment, including treatment interruptions, and for 4 weeks after completing treatment, and agree to do so.

Male patients may not donate semen or sperm during treatment with Revlimid and for 4 weeks following the discontinuation of Revlimid..

Prescribing and dispensing restrictions
For women of childbearing potential, prescriptions of Revlimid should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription.

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

Additional Precautions
Patients must be instructed never to give this medicinal product to another person and to return unused capsules to their pharmacist after the end of therapy. Patients must be instructed to not donate blood whilst taking Revlimid and for 4 weeks following the discontinuation of Revlimid.

Information material
In order to assist patients in preventing contact of unborn children with Revlimid, the marketing authorisation holder shall supply the following information material to health care professionals and patients:
- Medicinal product data sheet
- Information for health care professionals about the Pregnancy Prevention Programme for Revlimid
- Pregnancy prevention methods
- Patient brochure about the Pregnancy Prevention Program

Other Warnings and Precautions

Neutropenia and thrombocytopenia are among the most important dose-limiting toxicities of lenalidomide. For that reason, a complete blood count with differential blood count, platelet count, haemoglobin concentration and haematocrit should be performed once a week for the first 8 weeks of therapy, then once a month. A dose reduction may become necessary (see Dosage/Administration). Patients should be asked to inform the treating physician if there is any fever or bleeding, including petechiae and nosebleeds.

Lenalidomide has a strong immunosuppressant effect. Therefore, concomitant treatment with other immunomodulating agents should be undertaken only with caution. The effect of vaccinations may be impaired. Vaccinations with live organisms should not be given during treatment with lenalidomide due to the risk of infection.

Since hypothyroidism has been observed, thyroid hormone levels should be checked before starting treatment and during treatment.

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including previous thrombosis – should be closely monitored, and measures should be taken to minimise all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

The risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) is increased. Therefore there is a need to be especially alert to the symptoms of thrombosis or thromboembolism. Patients must be instructed to seek medical help if symptoms such as shortness of breath, cough, chest pain or pain and/or swelling of the arms and legs occur. Treatment with erythropoietic agents and hormone replacement therapy can increase the risk of thromboembolism and thus should not be given.

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide and dexamethasone is associated with an increased risk of venous thromboembolic events (primarily deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (primarily myocardial infarction and cerebrovascular events).

Consequently, patients with known risk factors for thromboembolism – including previous thrombosis – must be closely monitored. Measures should be taken to minimise all modifiable risk factors (e.g. smoking cessation, control of hypertension and hyperlipidaemia).

The decision whether to take antithrombotic prophylactic measures should be made after careful assessment for each patient individually.

If a thromboembolic event occurs, treatment with lenalidomide must be discontinued. Once the patient's condition has stabilised, treatment with lenalidomide may be resumed if required, with continuation of the anticoagulation.

Prolongation of the QTc interval has been observed on the ECG during treatment with lenalidomide. Concurrent treatment with drugs prolonging QT interval and treatment of patients with long QT syndrome should take place only with great caution and regular ECG monitoring.

Angioedema and severe dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. These events are potentially life-threatening. Discontinuation of Revlimid should be considered if there is the occurrence of a skin rash ≥ grade 2 with an exfoliative or bullous appearance or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Revlimid should not be resumed following discontinuation of the drug because of these reactions. Patients with severe grade 4 rash associated with thalidomide treatment should not receive Revlimid.

Tumour lysis syndrome (TLS) may occur. The patients at risk of tumour lysis syndrome are those with a high tumour burden prior to the start of treatment. These patients should be closely monitored, especially during the first cycle or dose-escalation and appropriate precautions taken.

Revlimid capsules contain lactose. Patients with a rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this drug.

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: 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 side effects 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 medications known to be associated with liver dysfunction.

Second Primary Malignancies

Based on a low number of cases, a numerical imbalance was observed in clinical trials in previously treated multiple myeloma patients with lenalidomide/dexamethasone compared with controls comprising mainly of basal cell and squamous cell skin cancers.

In clinical trials in newly diagnosed multiple myeloma patients, an increase of invasive second primary malignancies including AML, MDS and solid tumors has been observed with cases diagnosed in approximately 7.5% of patients receiving lenalidomide in combination with melphalan or immediately following high dose melphalan and ASCT compared with approximately 2.5% among controls. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting.

Take into account both the benefit achieved with lenalidomide and the risk of second primary malignancies before initiating treatment with lenalidomide. Carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

INTERACTIONS

Since lenalidomide is not metabolised via the phase I enzyme system and its plasma protein binding is low, interactions via the cytochrome P450 system and via protein binding are unlikely.

Since lenalidomide is eliminated by active tubular secretion, interactions with other drugs that are eliminated by active tubular secretion are possible. There is little experience in the case of elevated uric acid levels.

Lenalidomide (10mg) had no effect on the pharmacokinetics of R- and S-warfarin administered concurrently as a single dose. A single dose of 25 mg of warfarin had no effect on the pharmacokinetics of lenalidomide administered concurrently. However, it is not known whether there is an

interaction during clinical use. Close monitoring of the warfarin concentration is therefore advisable during treatment.
Treatment with coumarins is not recommended due to the high risk of thrombocytopenia.

Dexamethasone (40 mg/day) had no effect on the pharmacokinetics of Revlimid.

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.

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

PREGNANCY, LACTATION

There are no clinical data on the use of lenalidomide in pregnant women. Lenalidomide is structurally related to thalidomide. Thalidomide is a known teratogenic substance in humans that causes severe life-threatening birth defects. In an embryofetal development study in pregnant monkeys lenalidomide led to malformations in the offspring (see also “Preclinical Data”). A teratogenic effect of lenalidomide can be expected in humans. For details about the Pregnancy Prevention Programme: see “Warnings and Precautions“.

With regard to the treatment of male patients, see “Warnings and Precautions“.
It is not known whether lenalidomide is excreted in breast milk. For that reason Revlimid should not be used in breastfeeding mothers, or the infants should be weaned.

EFFECT ON ABILITY TO DRIVE AND OPERATE MACHINERY

No studies have been conducted on the effects on the ability to drive and operate machinery. Adverse effects such as fatigue, light-headedness, somnolence and blurred vision may occur on Revlimid. Therefore caution is advised when patients drive or operate machinery.

UNDESIRABLE EFFECTS

Multiple myeloma

In placebo-controlled phase III studies 353 patients received the lenalidomide/dexamethasone combination and 350 patients the placebo/dexamethasone combination. At least one side effect was observed in 325 patients (92%) in the lenalidomide/dexamethasone group, compared with 288 patients (82%) in the placebo/dexamethasone group.

The most serious undesirable effects observed were venous thromboembolism (deep vein thrombosis, pulmonary embolism) and grade 4 neutropenia.

The most frequently observed undesirable effects in the lenalidomide/dexamethasone group were neutropenia (39.4%; grade 4: 5.1%), thrombocytopenia (18.4%, grades 3-4: 9.9%), fatigue (27.2%), constipation (23.5%), muscle cramps (20.1%), asthenia (17.6%), anaemia (17.0%), diarrhoea (14.2%) and r ash (10.2%), insomnia (26.7%) and muscle weakness (10.1%). The occurrence of neutropenia and thrombocytopenia was mainly dose-dependent, and these conditions were successfully treated with dose reduction.

Myelodysplastic syndrome

In a pl acebo-controlled Phase III study 69 patients received 10 mg lenalidomide once daily and 67 patients received placebo.

The most serious undesirable effects observed were venous thromboembolisms (deep vein thrombosis, pulmonary embolism), grades 3-4 neutropenia, febrile neutropenia and grades 3-4 thrombocytopenia.

The most frequently observed undesirable effects in the lenalidomide group were neutropenia (76.8%; grades 3-4: 75.4%), thrombocytopenia (49.3%; grades 3-4: 40.6%), diarrhoea (37.7%), pruritus (27.5%), nausea (20.3%), fatigue (18.8%), constipation (17.4%), muscle spasm (17.4%), fever (15.9%), nasopharyngitis (14.5%), bronchitis (14.5%) and head-

ache (14.5%). The occurrence of neutropenia and thrombocytopenia was mainly dose-dependent and these conditions were successfully treated with dose reduction.

The side effects observed in patients with multiple myeloma and myelodysplastic syndrome are listed below by organ system and frequency. The side effects are stated in descending order of severity within each frequency group.
Frequency data: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare: (<1/10000).

Infections

Very common:	Nasopharyngitis (14.5%), bronchitis (14.5%), urinary tract infections (11.6%), upper respiratory tract infections (11.6%).
Common:	Local and systemic infections (bacterial, viral or fungal), pneumonia, oral candidiasis.
Uncommon:	Sepsis, atypical pneumonia, *Pneumocystis carinii* pneumonia, subacute endocarditis, ophthalmic herpes, herpes zoster, ear infections, oesophageal candidiasis.

Neoplasms

Uncommon:	Basal cell carcinoma, glioblastoma multiforme.

Blood and lymphatic system disorders

Very common:	Neutropenia (76.8%), thrombocytopenia (49.3%), anaemia (17.0%).
Common:	Febrile neutropenia, pancytopenia, lymphopenia, leucopenia.
Uncommon:	granulocytopenia, haemolytic anaemia, prolonged coagulation, monocytopenia, leucocytosis, lymphadenophathy.

Immune system disorders

Uncommon:	Acquired hypogammaglobulinaemia.
Uncommon:	*angioedema* ***(post-marketing experience).***

Endocrine Disorders

Common:	Cushingoid syndrome.
Uncommon:	Adrenal insufficiency, hypothyroidism, hyperthyroidism elevated or reduced TSH, hirsutism.

Metabolism and nutrition disorders

Very common:	Decreased appetite (10.1%).
Common:	Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention, weight loss, weight gain, iron overload.
Uncommon:	Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, gout, hypophosphataemia, hyperphosphataemia, increased appetite.

Psychiatric disorders

Very common:	Insomnia (26.7%).
Common:	Confusional state, hallucinations, depression, mood swings, fatigue, anxiety, irritability, drowsiness.
Uncommon:	Psychotic disorders, hypomania, delusions, decreased libido, personality changes, nervousness, aggression, nightmares.

Nervous system

Very common:	Headache (14.5%), dizziness (11.6%).
Common:	Cerebral ischaemia, syncope, peripheral neuropathy, light-headedness, disturbances of taste sensation, tremor, memory disorders, paraesthesia.
Occasional:	Cerebrovascular accident, leukoencephalopathy, polyneuropathy, speech disorders, attention deficit disorder, vestibular disorder, movement disorder, oral paraesthesia, psychomotor hyperactivity, anosmia, ataxia, dyskinesia, motor dysfunction, myasthenic syndrome.

Eye

Common:	Visual disturbances, cataract, increased lacrimation, conjunctivitis.
Uncommon:	Blindness, retinal arteriosclerosis, retinal venous thrombosis, keratitis, eye irritation, dry eye.

Ear and labyrinth

Common:	Vertigo.
Uncommon:	Deafness, hearing loss, tinnitus, earache.

Heart

Common:	Atrial fibrillation, *myocardial infarction* ***(post-marketing experience).***
Uncommon:	Congestive heart failure, heart valve incompetence, atrial flutter, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, pulmonary oedema, arrhythmia.

Vessels

Common:	Venous thromboses, deep vein thromboses, hypotension, hypertension, flushing, haematoma.
Uncommon:	Circulatory collapse, ischaemia, phlebitis.

Respiratory organs

Very common:	Cough (13.0%)
Common:	Pulmonary embolism, dyspnoea, hoarseness, hiccups, oropharyngeal pain, epistaxis.
Uncommon:	Asthma, chest pain.
Rare:	Interstitial pneumonitis.

Gastrointestinal disorders

Very common:	Diarrhoea (37.7%), constipation (23.5%), nausea (20.3%), abdominal pain (13.0%), vomiting (10.1%).
Common:	Dyspepsia, gastritis, abdominal distension, stomatitis, upper abdominal pain, dry mouth, flatulence.
Uncommon:	gastrointestinal bleeding, colitis, proctitis, dysphagia, haemorrhoids, oral pain, bleeding gums.
Rare:	*Pancreatitis* ***(post-marketing experience).***

Liver and bile

Common:	Abnormal liver function tests such as elevated alanine aminotransferase (ALT).
Uncommon:	Hepatic failure

Not known:	Acute hepatic failure, Hepatitis toxic, Cytolytic hepatitis, Cholytic hepatitis, Cholestatic hepatitis, Mixed cytolytic/cholestatic hepatitis

Skin

Very common:	Pruritus (27.5%), rash (13.0%), dry skin (10.1%).
Common:	Facial oedema, erythema, folliculitis, hyperpigmentation, exanthema, increased perspiration, hair loss.
Uncommon:	Erythema nodosum, urticaria, eczema, hyperkeratosis, skin fissures, acne, lichen sclerosus, photosensitivity reaction, burning skin sensation, desquamation.
Rare:	*Stevens-Johnson syndrome, toxic epidermal necrolysis* ***(post-marketing experience).***

Musculoskeletal system

Very common:	Muscle cramps (20.1%), muscle spasm (17.4%), skeletal muscle pain (13.0%), muscle weakness (10.1%).
Common:	Myopathy, peripheral swelling, backache, myalgia, arthralgia, limb pain.
Uncommon:	Osteonecrosis, muscle atrophy, muscle spasm, spondylitis, joint swelling, skeletal muscle stiffness, local swelling.

Kidneys and urinary tract

Common:	Renal insufficiency.
Uncommon:	Acute renal failure, frequent urination, renal tubular necrosis, urinary retention, acquired Fanconi syndrome, urinary incontinence.

Reproductive system and breast

Common:	Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain.

General disorders

Very common:	Fatigue (27.2%), asthenia (17.6%), fever (15.9%), peripheral oedema (13.0%).
Common:	Falls.
Uncommon:	Thirst, cold sensation.

To report any side effect(s):

· **Saudi Arabia:**

- National Pharmacovigilance and Drug Safety Center (NPC)
  Call NPC at +966-11-2038222,
  Exts: 2317-2356-2353-2354-2334-2340
  - Fax: +966-11-205-7662
  - Toll-free: 8002490000
  - Email: npc.drug@sfda.gov.sa
  - Website: www. sfda.gov.sa/npc

OVERDOSE

In the studies, the dose-limiting toxicity was essentially haematological.
In the event of overdose, monitoring (clinical, laboratory) as well as supportive measures are indicated.
Lenalidomide is only slightly dialysable.

PROPERTIES/EFFECTS

ATC Code: L04AX04.

Mechanism of action /Pharmacodynamics
Lenalidomide is a derivative of thalidomide and exists as a racemate. It possesses both immunomodulating and antiangiogenic properties.

Lenalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and Roc1, and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may explain the pleiotropic cellular effects observed with lenalidomide treatment.

Lenalidomide inhibits the release of proinflammatory cytokines including tumour necrosis factor α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-12 from the lipopolysaccharide (LPS)–stimulating mononuclear cells of the peripheral blood and increases the formation of the anti-inflammatory cytokine IL-10 in LPS-stimulated cells.
It induces the production of IL-2 and interferon-1γ (IFN-1γ) and increases the proliferation of T cells as well as the cytotoxic activity of the natural killer cells.

Lenalidomide inhibits the proliferation of various haematopoietic tumour cell lines.

In *in vitro* angiogenesis models lenalidomide inhibits angiogenesis by preventing the development of microvessels and endothelial cell channels as well as the migration of endothelial cells. In addition, lenalidomide inhibits the formation of proangiogenic factors VEGF in PC3 prostate tumour cells.

Cardiac Electrophysiology QT study
At single doses of 10 mg or 50 mg of lenalidomide in healthy male subjects, no prolongation of the QTc interval could be associated.

Clinical Efficacy
Clinical experience in multiple myeloma
In two multicentre, randomised, placebo-controlled, parallel group controlled, double-blind studies of identical design (MM-009 in the USA and Canada or MM-010 in Europe, Israel and Australia) 353 and 351 patients, respectively, with multiple myeloma, previously treated with one or more chemotherapy regimens, were treated either with lenalidomide plus dexamethasone or with dexamethasone alone.

In a pooled analysis of both studies, the median time to progression (TTP) was 48.3 weeks (95% CI: 41.1; 60.1) in patients treated with lenalidomide/dexamethasone and 20.1 weeks (95% CI: 19.9, 20.7) in patients treated with placebo/dexamethasone. The median duration of progression-free survival was 47.3 weeks (95% CI: 36.9, 58.4) *versus* 20.1 weeks (95% CI: 18.1, 20.3). The overall survival in patients treated with lenalidomide/dexamethasone was significantly higher at 90.3 vs 80.2 weeks, p=0.015, (patients in the placebo arm could, after progression and after unblinding, change to the active arm; 50% were treated with lenalidomide/dexamethasone).
The median duration of treatment was 28.1 weeks (min: 0.1, max: 110.7).

Clinical experience in myelodysplastic syndrome
In a multicentre, single-arm, open phase II study (MDS-003 in Germany and the USA), 120 patients with confirmed erythrocyte transfusion dependence due to MDS with a low or intermediate risk 1 with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities

were treated with lenalidomide 10 mg. The median duration of treatment was 52.5 weeks. The rate of transfusion-independence (> 56 days) was 62.8%. The median increase in haemoglobin was 5.9 g/dl. The median duration of response was 97 weeks. A clear cytogenetic response was observed in 34.6% of the patients and a less pronounced cytogenetic response was observed in 38.5% of the patients.

In a multicentre, double-blind, placebo-controlled, three-arm phase III study (MDS-004 in Europe and Israel), 138 patients with confirmed erythrocyte transfusion dependence due to MDS with a low or intermediate risk 1 with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities were treated with lenalidomide 10 mg, lenalidomide 5 mg or placebo, according to randomisation. The duration of the double-blind phase was 16-52 weeks. The rate of transfusion-independence (> 182 days) was 56.1% in the 10 mg group. The corresponding transfusion-independence rates in the 5 mg and placebo groups were 41.3% and 5.9%, respectively. The median duration of repsonse was 106 weeks in the 10 mg group; in the 5 mg and placebo groups, in contrast, it could not be determined. A clear and less pronounced cytogenetic response was observed in 24.0% and 17.1% of the patients, respectively, in the 10 mg group, 10.9% and 6.5%, respectively, in the 5 mg group and 0% and 0%, respectively, in the placebo group.

The rate of transfusion-independence (> 56 days) in the 10 mg group was 61.0%, with a median increase in haemoglobin of 6.3 g/dl. The corresponding transfusion-independence rates and haemoglobin increases in the 5 mg and placebo groups were 50.0% and 7.8%, respectively, and 5.1 g/dl and 2.3 g/dl, respectively.

PHARMACOKINETICS

Absorption

Lenalidomide is rapidly absorbed with a T_{max} of 1 hour. The oral bioavailability is about 70%. Simultaneous administration with food leaves the extent of absorption unchanged. The $T_{max,}$ however, is prolonged and C_{max} reduced by 36%. The pharmacokinetics of lenalidomide are dose-proportional.

Distribution

The binding of lenalidomide to plasma proteins is low (<30%). The volume of distribution is 80 l. It has not been investigated whether or not lenalidomide crosses the blood-brain barrier.

Lenalidomide is present in semen (< 0.01% of the dose) after administration of 25 mg/day. Lenalidomide is undetectable in the semen of healthy volunteers 3 days after discontinuation of the medicinal product.

Metabolism

Lenalidomide is partially metabolised, with metabolism not occurring via the phase I enzymes. Unchanged lenalidomide is the main circulating component *in vivo* in humans. Two identified metabolites are hydroxyl-lenalidomide and N-acetyl-lenalidomide; each constituting less than 5% of the blood levels of the parent substance.

Elimination

Approximately two thirds of a dos e of lenalidomide is eliminated unchanged via the kidneys. Lenalidomide is actively eliminated by tubular secretion.

The clearance is 300 ml/min.

The elimination half-life is about 3 hours for a single dose and 7.6 hours for multiple doses. Steady state concentrations are reached on day 4. Accumulation does not occur with multiple doses.

Kinetics in special patient groups

There are no data available about the pharmacokinetics in p aediatric patients.

Lenalidomide is eliminated primarily as an unchanged active substance via glomerular filtration and active tubular secretion. After a single dose of 25 mg in mild renal insufficiency (ClCr 80-50 ml/min), the AUC is increased by 25%; in moderate renal insufficiency (ClCr 50-30 ml/min) the AUC is increased 3-fold, and in severe renal insufficiency (ClCr <30 ml/min) and/or renal insufficiency requiring dialysis (interdialysis period) the AUC is increased 4- to-5-fold. The elimination half-life is increased in moderate renal insufficiency 3-fold to 9-10 hours.

Pharmacokinetics in patients with hepatic insufficiency

Population pharmacokinetic analysis included patient with weak hepatic insufficiency (N=16; total bilirubin >1, bis ≤ 1,5 x ULN or AST > ULN) and showed that a week hepatic insufficiency doesn't influence the

Lenalidomide disposition. No data are available for patient with moderate to heavy hepatic insufficiency.

PRECLINICAL DATA

Lenalidomide demonstrates a low potential for acute toxicity; in rodents the lowest lethal doses after oral administration were more than 2000 mg/kg. Long-term administration of lenalidomide to rats led, most conspicuously in female animals, to mineralisation of the renal pelvis. The dose at which no side effects occurred (*no observed adverse effect level,* NOAEL), is estimated to be less than 75 mg/kg for rats and thus, based on the AUC, is about 25 times higher than the daily human exposure at a dose of 25 mg/day. In monkeys, repeated oral administration led to a dose-dependent decrease in the neutrophil count; this effect is due to the pharmacodynamic action of the active substance. Repeated oral administration of 4 and 6 mg/kg to monkeys over a period of up to 20 weeks led to mortality and significant toxicity (marked weight loss, decreased red and white blood cell counts as well as a decrease in the platelet count, multiple organ haemorrhage, inflammation of the gastrointestinal tract, atrophy of the lymphatic tissue and the bone marrow). Administration of 1 and 2 mg/kg/day to monkeys for 52 weeks led to changes in the cell count of the bone marrow, a slight decrease in the ratio of myeloid to erythroid cells and to thymus atrophy. At 1 mg/kg/day a slight suppression of the leukocyte count was observed. The NOAEL was 1 mg/kg/day. The AUC exposure at this dose corresponds to human therapeutic exposure at 25 mg/day.
Mutagenicity studies *in vitro* (bacterial mutations, human lymphocytes, mouse lymphoma, Syrian hamster embryo cell transformation) and *in vivo* (micronucleus test in rats) showed no effects of the active substance either at the genetic level or at the chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity (embryofetal toxicity/teratogenicity) studies were conducted in rats, rabbits and monkeys. In a study in monkeys, lenalidomide was administered in doses of up to 4 mg/kg/day. The results show that the administration of lenalidomide to pregnant monkeys led to malformations in the offspring which were similar to the malformations produced by thalidomide.

In rabbits that received oral doses of 3, 10 and 20 mg/kg/day, developmental toxicity at 10 and 20 mg/kg/day was characterized by slightly reduced fetal body weight, an increased incidence of post implantation loss (early and late resorption and intrauterine death) and macroscopic external findings in the fetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body). At 10 and 20 mg/kg/day, fetuses were observed to have soft tissue and skeletal changes but which are typical of the strain of rabbit used. In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day.

As is known from previous thalidomide studies in rats, an embryo-fetal development study in rats with lenalidomide doses up to 500 mg/kg/day also revealed no teratogenic effects. At 100, 300 or 500 mg/kg/day there was minimal maternal toxicity that included a slight, transient reduction in mean body weight gain and food intake.

FURTHER INFORMATION

Shelf life

The medicinal product may not be used after the expiry date stated on the container after EXP.

Special instructions for storage

Store below 30°C. Store in the original package and out of the reach and sight of children.

Instructions for handling

As with cytostatics, special care is required in the handling and disposal of Revlimid (see also “Dosage/Administration“).

PACKS

Revlimid 5 mg: 21 hard capsules (A)

Revlimid 10 mg: 21 hard capsules (A)

Revlimid 15 mg: 21 hard capsules (A)

Revlimid 25 mg: 21 hard capsules (A)

MARKETING AUTHORISATION HOLDER

Celgene International Sàrl, Boudry, Switzerland

DATE OF LAST REVISION

July 2014

i-SECURE

Adverse Events

Revlimid® (Lenalidomide)

Date Received by Biologix	Local Tracking N°	Page 1 of 3

1. Patient Details

Initials	Sex	Date of Birth
	Female ☐ Male ☐ Unk ☐	
Weight (kg)	Height (cm)	Race .....
Pregnant ?	No ☐ Yes* ☐ NA ☐ Unk ☐	
* Please give details in sections 8 or 11.		

2. Reporter Details : (Complete reporter details required for HCP, if Patient reporter just choose patient in the occupation section and state the country)

Name (For HCP) or Initials (for patient)	Occupation : .....
Address :	
Country :	Fax :
Phone 1 :	Email :
Phone 2 :	

3. Relevant Medical History : (Include primary diagnosis and preexisting medical conditions)

.....

4. Adverse Event Terms : *Relationship – only for HCP reports

"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?
"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?
"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?
"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?
"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?
"AS REPORTED TERM"					
Date Started	Date Stopped	Outcome	Relationship*	Prior History?	Serious?

5. Suspect Product (Include all cycles. Please record details of any dose reductions or increases)

Drug Name :	Vial Size :	Lot N°(s) :	Indication for Use :

Start Date	Stop Date	Dose	Units	Route	Frequency	Additional Comments

6. Action Taken on Suspect Product : (Please tick the appropriate boxes and record the dates if applicable and available) ☐ Unk

☐ None	☐ Dose Reduced	☐ Dose Increased	☐ Temporarily Withdrawn	☐ Permanently Withdrawn	☐ Discontinued (NOS)*

Dates :	Drug Reintroduced ☐ Yes ☐ No
Date of last dose prior to discontinuation	Date :

(NOS) = not otherwise specified

Date Received by Biologix	Local Tracking N°	Page 2 of 3

7. Serious Criteria : (Please tick all appropriate boxes)

1. Fatal ☐	2. Persistant/Significant Disability ☐	3. Hospitalisation ☐	4. Medically Significant ☐	5. Congenital Abnormality ☐

1a. Date of Death :	3a. (Initial or Prolonged)
1b. Cause of Death :	3b. Admission Date :
	3c. Discharge Date :

8. Describe Event(s) :	Give a chronological summary of signs and symptoms. Please provide diagnosis, treatment, outcome, and autopsy details, if appropriate.
Initial report date :	.....
Follow-up 1 report date :	.....
Follow-up 2 report date :	.....
Follow-up 3 report date :	.....

9. Concomitant Medications :

Drug Name	Route	Dosage Units & Freq.		Start Date	Stop Date	Suspect Yes or No		Indication
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	

Date Received by Biologix	Local Tracking N°	Page 3 of 3

10. Corrective Treatments (given for the event)

Drug Name	Route	Dosage Units & Freq.		Start Date	Stop Date	Suspect Yes or No		Indication
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	
						☐	☐	

11. Relevant Diagnostic Tests: (Please provide the name, date, results and normal values for all diagnostic tests performed)

Name	Date	Results	

Comments on tests:	

Name of Recorder	Signature	Date

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Pregnancy Capture Form

Revlimid® (Lenalidomide)

Please complete this form to report a pregnancy in a patient (or in a female partner of a male patient) treated with lenalidomide. Please send immediately to Biologix, SFDA Pharmacovigilance Center and/or Celgene.
As part of Biologix risk management plan (i-SECURE), it is essential to report all pregnancies for adequate follow-up. Biologix/Celgene will therefore be in contact with you for further information in due course and would value your cooperation to ensure we are able to obtain all relevant information regarding foetal exposure to lenalidomide.
To report a pregnancy please contact:

1.Pharmacovigilance

Salehiya at: Ph. Mohammed Waqas- Pharmacovigilance Representative -
Salehiya Trading Establishment - E-Mail : m.waqas@salehiya.com - PO Box 991, Riyadh 11421- - Kingdom of Saudi Arabia - Tel #+966 1 1464 6955 Ext 362

The National Pharmacovigilance and Drug Safety Centre (NPC)
-Fax: +966-11-205-7662
-Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340
-Toll free phone: 8002490000
-E-mail: npc.drug@sfda.gov.sa
-Website: www.sfda.gov.sa/npc

Reporter Information			
Reporter Name:		Occupation:	
Address:		City, Country:	
Phone No.: Fax No.:		Email address:	
Female Patient Information			
ID:	Age:	Date of Birth:	
Female Partner of Male Patient			
ID:	Age:	Date of Birth:	
Patient Treatment Information: Lenalidomide Capsule			
Batch No.:	Expiry Date:	Dose:	Frequency:
Start Date:		Stop Date:	
Indication for Use:			

Follow-up of the Pregnancy	Yes	No
Has the patient already been referred to an Obstetrician/Gynecologist		
If yes, please specify his/her name and contact details		
Reason for Failure of Pregnancy Prevention Program	**Yes**	**No**
Was patient erroneously considered not to be of childbearing potential		
If yes, state reason for considering not to be of childbearing potential		
a. Age 50 years and naturally amenorrhoeic for 1 year		
b. Premature ovarian failure confirmed by a specialist gynecologist		
c. Previous bilateral salpingo-oophorectomy, or hysterectomy		
d. XY genotype, Turner syndrome, uterine agenesis		
Indicate from the list below which contraception was used	**Yes**	**No**
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	**Yes**	**No**
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 material 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 Obstetric 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			

If yes to either of these questions, please provide details below

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Maternal Past Medical History				
Condition	Dates		Treatment	Outcome
	From	To		

Maternal Current Medical Conditions		
Condition	Date	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