Physicians Information

Lenalidomide Teva® (Lenalidomide)
RMP- Risk Management Plan
PPP- Pregnancy Prevention Program

teva

Table of content:

Please note: additional educational materials and forms of the program (not included in this brochure):

- **Patient Educational Materials** (brochures in Hebrew, Arabic, Russian and English)
- **Program Registration Forms** for:
  - Physician
  - Pharmacy
  - Patient- to be filled-in by the physician and signed by the physician and patient (patient section available in Hebrew, Arabic, Russian and English)
- **Pregnancy Reporting Form**
- **Pregnancy Test Results Form**

For full information please refer to Lenalidomide PI as approved by IL MOH

About Lenalidomide:

Lenalidomide belongs to the Pharmacotherapeutic group of "Other immunosuppressants" (ATC code: L04AX04).

The Lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, proerythropoietic, and immunomodulatory properties.

Lenalidomide Teva is indicated for:

- Previously untreated multiple myeloma (MM) in adult patients who are not eligible for transplant.
- In combination with dexamethasone treatment of multiple myeloma patient who have received at least one prior therapy.
- Patients with 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.
- The treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

The Teratogenicity of Lenalidomide

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

Obligations of the Health Care Professional in Relation to the Prescribing of Lenalidomide

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

The prescriber should provide comprehensive advice and counselling to patients.

The prescriber must ensure that for women of childbearing potential (patients or patients' partners):

- The woman complies with the conditions of the Pregnancy Prevention Program, including confirmation that she has an adequate level of understanding.
- The woman has acknowledged the aforementioned conditions.

The prescriber should provide patients with appropriate patient educational brochure.

Maximum duration of a prescription is 4 weeks.

Criteria for women of non-childbearing potential

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

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 year (24 months) (amenorrhoea following cancer therapy or during breastfeeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, or hysterectomy.
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

Safety advice for women of childbearing potential:

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

- She was explained the expected teratogenic risk to the unborn child
- She was explained the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She was explained that once established on contraception for 4 weeks the patient is required to have a medically supervised negative pregnancy test. The first prescription for Lenalidomide can only be given after one negative medically supervised pregnancy test
- She was explained the need to commence the treatment as soon as Lenalidomide is dispensed following a negative pregnancy test
- She was explained the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she was explained the hazards and necessary precautions associated with the use of Lenalidomide

- If she becomes pregnant whilst taking Lenalidomide, she should stop therapy and inform her treating physician immediately. It is recommended to refer the partner to a physician specialised or experienced in teratology for evaluation and advice

Safety advice for men

For male patients taking Lenalidomide, pharmacokinetic data has demonstrated that Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject. As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, **all male patients taking Lenalidomide must meet the following conditions:**

- He was explained the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- He was explained the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 4 week after dose interruptions and/or cessation of treatment
- He was explained that if his female partner becomes pregnant whilst he is taking Lenalidomide or shortly after he has stopped taking Lenalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice

Contraception

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

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot

- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking Lenalidomide in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking Lenalidomide monotherapy, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.
Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy Testing

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

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when Lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test

should ensure the patient is not pregnant when she starts treatment with Lenalidomide.

Follow-up and end of treatment

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

Requirements in the event of pregnancy

Upon suspicion of pregnancy during Lenalidomide therapy (or within 4 weeks from stopping treatment), the prescriber should inform Teva immediately. The pregnancy report (while on Lenalidomide therapy) should be provided by filling-in the Pregnancy reporting form.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to Lenalidomide, the marketing authorisation holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of Lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure. A national controlled distribution system has been implemented in collaboration with the Ministry Of Health. The controlled distribution system includes the use of a patient card, a prescribing brochure and dispensing controls.

Other Information:

Posology and Method of Administration

Lenalidomide treatment should be supervised by a physician experienced in the use of anti-cancer therapy.
Dose should be modified based upon clinical and laboratory tests.

Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to Lenalidomide.
In case of neutropenia, the use of growth factors in patient management should be considered.

If less than 12 hours has elapsed since missing a dose, the patient can take the dose.
If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

For other grade 3 or 4 toxicities judged to be related to Lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.
Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash.
Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions.

REFERENCES

1. CHMP position on the PRAC PSUR Assessment Report for Lenalidomide (EMEA/H/C/ PSUSA/00001838/201512), issued in 2016.
2. CHMP position on the PRAC PSUR Assessment Report for Lenalidomide (EMEA/H/C/ PSUSA/00001838/201612), issued in 2017.
3. PRAC recommendation on signals from May 2018 (EMA/PRAC/287231/2018), issued in June 2018.

Check List for Physicians

_____	I have explained this to my patient [YES/NO]
Is Lenalidomide prescribed to the patient in line with its approved indication?	
The patient was explained that Lenalidomide is a derivative of Thalidomide known to cause severe birth defects and that they must not get pregnant whilst taking it.	
The patient was explained that: **For male patients:** Patient must use condoms during Lenalidomide therapy and 4 weeks after stopping therapy. **For female patients or when a male patient cannot use condoms**: She/the female partner must consistently and correctly use 2 highly effective method of contraception (i.e. a user-independent form such as an intra-uterine device or implant) or 2 complementary methods of birth control (i.e. user-dependent forms such as oral contraceptive and barrier method) before and during treatment.	
The patient was explained that the risk persists even after the medication is stopped and that she must not get pregnant within: **Female patients:** 4 weeks after stopping treatment. **Male patients:** 4 weeks after stopping treatment.	
The patient has received advice on contraception which is appropriate for her and has committed to using it throughout the risk period.	
The patient is aware of the risk of contraceptive failure.	
Once established on contraception for 4 weeks the patient is required to have a medically supervised negative pregnancy test. The first prescription for Lenalidomide can only be given after one negative medically supervised pregnancy test. This is to make sure she is not already pregnant before starting treatment.	
Patient was explained that in order to support regular follow up, including pregnancy testing and monitoring, the prescription should be limited to 28 days.	

Patient was explained that Lenalidomide prescription should be signed no later than 3 days from the negative pregnancy test Dispensing of Lenalidomide to women of childbearing potential should occur within 7 days of the prescription.	
Patient was explained the need for and agrees to pregnancy testing before, during and after treatment.	
Patient was explained the need for periodic pregnancy tests with 28 days intervals throughout treatment and also for a period of 4 weeks after stopping treatment. This is because the drug can stay in the body for 4 weeks after the last dose and can damage an unborn baby if pregnancy occurs.	
The patient has received a copy of the educational package.	
The patient was explained that, according to Israeli ministry of health requirements, Lenalidomide is under controlled distribution program and that information regarding all patients and prescriptions is collected by Teva. The information might be shared with the ministry of health and other applicable bodies, per regulatory requirements.	
The patient knows to contact the doctor if they have unprotected sex, miss their period, become pregnant, or suspect that they have become pregnant during the risk period.	
If pregnancy occurs, treatment must be stopped and the patient should be referred to an expert physician specialised or experienced in teratology for advice.	
Patient was explained that Lenalidomide has been prescribed to her only and must not be shared with others.	
Patient was explained that she must not donate blood during treatment with Lenalidomide and for 4 weeks after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	

Reports on Pregnancy during Treatment with Lenalidomide Teva should be sent to the following Parties:

To the Ministry of Health:

By the portal of side effects reporting at the homepage of the Ministry of Health website **www.health.gov.il** or by entering the link:
/https://sideeffects.health.gov.il

To Teva Pharmaceutical Industries Ltd.:

By Email: **Safety.Israel@teva.co.il**
By Phone: **03-6864000**
By Fax: **03-9127870**

The above contacts can be also used for reporting adverse events during the treatment with Lenalidomide Teva.

Information for physicians, the treatment staff, patients and pharmacists about the use of personal information – risk management program relating to the administration of the drug Lenalidomide

Teva Pharmaceutical Industries Ltd. (hereinafter: "**Teva**" or "**we**") respects your right to privacy. Your ability to make informed decisions about the use of information belonging to you is important to us. In this document, we specify the information that we collect from you, how we protect it and what uses we make of the information.

Information that we collect

"Personal information" is information that can be attributed to a person or entity, such as a name, address or medical information. The personal information that we collect is collected through the completion of a paper or online registration form for the risk management program (the form is completed by the patient, the treating physician or the pharmacist), which includes, inter alia, name, identity card number (or other identification number), date of birth, membership in an HMO, medical condition and diagnosis, state of pregnancy and/or fertility, the type of treatment and medicines, language preferences, details about parents and/or guardians and/or participation in instructional sessions. The personal information that we collect from physicians, the treatment staff and/or from pharmacists through their completion of the program registration form includes name, institutional affiliation, occupation, license number, telephone number and e-mail address. We also collect any additional personal information that will be provided by patients, physicians, treatment staff and pharmacists in the future within the framework of the risk management plan. We also collect any additional personal information that you provide to us now or in the future. It is your voluntary decision whether or not to provide us with particular information, but we must collect and retain some of the information in order to comply with the statutory and regulatory requirements.

How we protect the information

We employ commercially reasonable and accepted information-security measures to protect the information furnished to us, but there are no electronic transfer or storage methods that are absolutely secure. Therefore, although we try to employ maximum measures to protect your information, we cannot guarantee the absolute security of the information.

How we use the information

We will not share your information with any other parties without your express consent, apart from in ways explicitly referred to here, unless we will be required to do so pursuant to any law, regulation or court order or for the purpose of cooperating with an investigation by the law enforcement authorities. The main purposes for collecting and saving the information about you are for the participation in risk management programs as is required by law and regulation, for the operation of this program and for the controlled dispensing of the medicine within its framework. We will share the information with the authorized authorities for the purpose of complying with these requirements.

We use external companies as our subcontractors in order to provide us with services relating to the personal information, including in order to participate in a risk management program, and in order to store the personal information on their servers, which will be operated on our behalf. All of the subcontractors that will operate on our behalf will be subject to obligations regarding the use of information and to the obligations by law. We might transfer our databases, which contain your information, if we sell our business or a portion thereof, including while negotiating the sale and including during liquidation but, in such instance, the recipients of the information will undertake to safeguard confidentiality and to act in compliance with the relevant provisions specified in this document.

Right to peruse and amend

You have a right to demand to peruse your information or to update or correct it in particular instances. If you wish to do so, please contact us at [IL_Privacy.Tevail@teva.co.il]. If you have any questions about this privacy policy, if you do not agree to that stated therein or if you wish to contact us about any other matter, please contact us at [IL_Privacy.Tevail@teva.co.il].

I have read the document “Information for physicians, the treatment staff, patients and pharmacists about the use of personal information – risk management program relating to the administration of the drug Lenalidomide” and I agree to that stated therein.

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דיווחי היריון במהלך טיפול בלנלידומיד טבע יש לשלוח לגורמים הבאים:

- **למשרד הבריאות** - באמצעות פורטל לדיווח על תופעות לוואי שנמצא בדף הבית של אתר משרד הבריאות www.health.gov.il או ע"י כניסה לקישור: https://sideeffects.health.gov.il/
- **לחברת טבע תעשיות פרמצבטיות בע"מ** - במייל: Safety.israel@teva.co.il בטלפון: 03-6864000 בפקס: 03-9127870

להתוויות ולמידע נוסף אודות התכשיר כנון: תופעות לוואי, יש לעיין בעלון העדכני כפי שאושר ע"י משרד הבריאות.
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