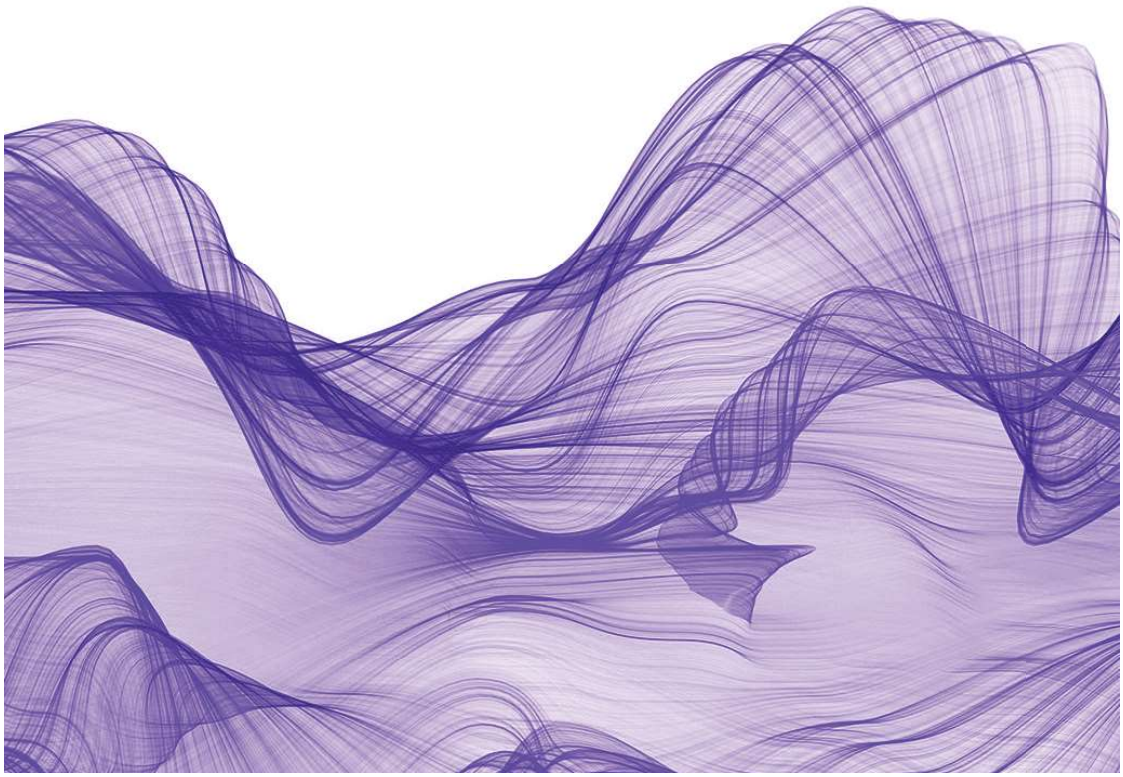
K.S. KIM INTERNATIONAL

Healthcare Professional's Information Booklet Lenalidomide S.K.

RMP- Risk Management Plan

PPP- Pregnancy Prevention Program



This pack contains the information and materials needed for prescribing and dispensing Lenalidomide S.K. according to the Pregnancy Prevention Program.

It is a requirement of the Pregnancy Prevention Program that all healthcare professionals ensure that they have read and understood this pack before prescribing or dispensing Lenalidomide S.K. for any patient. Lenalidomide S.K. is structurally similar to thalidomide, a known human teratogenic substance that causes severe life-threatening birth defects. Lenalidomide induced, in monkeys, malformations similar to those described with thalidomide.

If Lenalidomide S.K. is taken during pregnancy, a teratogenic effect of Lenalidomide in humans is expected. Lenalidomide S.K. is therefore contraindicated in pregnancy and in women of childbearing potential.

Disclaimer: This information pack **only** refers to Risk Management Plan (RMP), Pregnancy Prevention Program (PPP), to find out more about the medication, side-effects and warnings please refer to SmPC of the product.

Contents

Personal Information

Information for patients, doctors, caregivers & pharmacists about the use of personal information – risk management program relating to the administration of the drug Lenalidomide

K.S. Kim International Ltd. (hereinafter: "K.S. Kim" 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 from patients includes name/ initials, 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, details about parents and/or guardians and/or participation in instructional sessions. 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 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 purpose for collecting and saving the information about you is to participate in risk management programs as is required by law and regulation. We will share the information with the authorized authorities for the purpose of complying with these requirements.

We use an external company as a subcontractor 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. All of the subcontractors will be subject to nondisclosure and non-use of information obligations. 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.

Right to peruse and amend

You have a right to demand to peruse your information or to update or correct it. If you wish to do so, please contact us at lenalidomide@sk-pharma.com. 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 lenalidomide@sk-pharma.com.

I have read the document "Information for patients, doctors, caregivers & 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.

What is Lenalidomide S.K.

Lenalidomide S.K. belongs to the Pharmacotherapeutic group of "Other immunosuppressants"

The Lenalidomide S.K. mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties.

Lenalidomide S.K. is indicated for:

- The maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who have undergone autologous stem cell transplantation.
- Previously untreated multiple myeloma in adult patients who are not eligible for transplant.
- In combination with dexamethasone treatment of multiple myeloma patients who have received at least one prior therapy.
- Patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
- Lenalidomide S.K. 7.5 mg is **not indicated** for treatment in MDS.
- The treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

Posology and method of administration

Lenalidomide S.K. treatment should be supervised by a specialist oncology physician. Dose should be adjusted based upon clinical and laboratory tests.

Lenalidomide S.K can cause significant neutropenia and thrombocytopenia.

Toxicity - Dose Adjustments

- To manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to Lenalidomide S.K., Dose adjustments, during treatment and restart of treatment, are recommended.
- In case of neutropenia, the use of growth factors in patient management should be considered.
- For other grade 3 or 4 toxicities judged to be related to Lenalidomide S.K., treatment should be stopped and only when toxicity has resolved to ≤ grade 2, can be restarted at the next lower dose level, depending on the physician's discretion.
- Lenalidomide S.K. interruption or discontinuation should be considered for grade 2 or 3 skin rash.

Toxicity – Discontinuation of Treatment

If any the following are suspected, Lenalidomide S.K. must be discontinued and should not be resumed even post recovery from these reactions:

- angioedema,
- grade 4 rash,
- exfoliative or bullous rash,
- Stevens-Johnson syndrome (SJS),
- toxic epidermal necrolysis (TEN) or
- Drug Reaction with Eosinophilia & Systemic Symptoms (DRESS)

Missed Doses

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.

Pregnancy Prevention Program (PPP)

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.

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.
It is a requirement of the Pregnancy Prevention Programme that all healthcare professionals ensure that they have read and understood this pack before prescribing or dispensing Lenalidomide S.K. for any patient.

In order to ensure that the actions to minimise the risk of foetal exposure are carried out for all patients, only doctors that are registered to the program, can prescribe Lenalidomide S.K., dispensing of Lenalidomide S.K. will only be allowed from pharmacies registered with K.S. Kim International Ltd. (K.S. Kim). K.S. Kim will not authorise supply of Lenalidomide S.K. to pharmacies that are not registered.

To register, **"**Doctor Registration form**"** & "Responsible Pharmacist/Pharmacy Registration Form" will need to be completed and acknowledged by K.S. Kim.

The following are core requirements of the Pregnancy Prevention Programme:

- All healthcare professionals dispensing or prescribing Lenalidomide S.K. must read the Lenalidomide S.K. "Healthcare Professional's Information Booklet."
- All pharmacies who dispense Lenalidomide S.K. must agree to implement risk minimisation by registering with K.S. Kim using the "Responsible Pharmacist/Pharmacy Registration Form".
- All prescriptions for Lenalidomide S.K. must be accompanied by a Lenalidomide S.K. "Monthly Pregnancy Test Form", a copy of which must be sent to K.S. Kim, **unless** the doctor has declared in the "Patient Registration Form" that the patient is exempt.

- The prescribing doctor must provide advice and counselling to all patients.

- 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 prescribing doctor must ensure to advise both patients and patients' partners, so that all women of childbearing potential, fully understand all the precautions and the risks regarding Lenalidomide S.K. to ensure they comply with the conditions of the Pregnancy Prevention Program, including confirmation that they have an adequate level of understanding.

- The prescribing doctor should provide patients with the "Patient Information Booklet" and patients should complete and sign the "Patient Registration Form" together with the prescribing doctor confirming their awareness of the risks of the treatment in regard to foetal exposure.

- Maximum duration of a prescription is 4 weeks for patients required to perform monthly pregnancy tests.

Documents available for the Pregnancy Prevention Program

- **Healthcare Professional's Information Booklet**
- **Patient Information Booklet**
- **Doctor's Registration Form**
- **Responsible Pharmacist/Pharmacy Registration Form**
- **Patient Registration Form**
- **Monthly Pregnancy Test Form**
- **Pregnancy Report**

Management to Avoid Foetal Exposure

All patients should be advised that if a pregnancy does occur whilst they are receiving Lenalidomide S.K.:

1. **If the patient is pregnant, she must immediately stop treatment.**
2. **If the patient or the patient's partner is pregnant, they must inform their physician immediately.**

Women of non-childbearing potential

Women are only considered not to have childbearing potential and do not need to undergo pregnancy testing or receive contraceptive advice, if they fall under the following categories:

- Age 50 years and older and naturally amenorrhoeic for more than 24 months.
    - Please note amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, tubal sterilisation or hysterectomy.
- XY genotype, Turner syndrome, uterine agenesis.

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

Women of childbearing potential

In view of the expected teratogenic risk of Lenalidomide S.K., foetal exposure should be avoided. Women of childbearing potential (even if they have amenorrhoea) must:

- **EITHER** Use two effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after Lenalidomide S.K. therapy, and even in case of dose interruption
- **OR** Commit to absolute and continuous sexual abstinence – this will need to be confirmed on a monthly basis.

Once established on contraception for 4 weeks the patient is required to have medically supervised negative pregnancy tests. The initial test should be performed prior to beginning therapy within 3 days prior to prescribing Lenalidomide S.K. and then monthly thereafter (including dose interruptions) and 4 weeks after the end of therapy (unless confirmed tubal sterilisation).

This also includes those women of childbearing potential who confirm absolute and continued sexual abstinence.

There must be no more than **3 days** between the dates of the last negative pregnancy test and the prescription.

- Best practice is for the pregnancy test, prescribing and dispensing to take place on the same day.
- Dispensing of Lenalidomide S.K. to women of childbearing potential should occur within 7 days of the prescription.

Lenalidomide S.K. is contraindicated in women of childbearing potential, unless all the following are met:

1) The expected teratogenic risk to the unborn child has been explained.
2) The patient has the capacity to comply with effective contraceptive measures.
3) The patient understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment.
4) Even if a woman of childbearing potential has amenorrhea, she must follow all the advice on effective contraception.
5) The patient should be capable of complying with effective contraceptive measures
6) The patient understands the need to commence the treatment as soon as Lenalidomide S.K. is dispensed following a negative pregnancy test.
7) The patient understands and accepts necessity to undergo pregnancy testing every 4 weeks.
8) The patient is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
9) The patient also confirms that if she becomes pregnant whilst taking Lenalidomide S.K., 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.
10) The patient confirms that the hazards and necessary precautions associated with the use of Lenalidomide S.K. was explained by the prescribing doctor.

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 healthcare professional for contraceptive advice to initiate contraception.

The patient must consistently and correctly use two highly effective method of contraception

- One highly effective form of contraception
  - tubal ligation,
  - IUD,
  - hormonal (birth control pills, Injections, hormonal-patches, vaginal rings, or implants), **or**
  - partner's vasectomy,

AND

- One additional effective contraceptive method
  - male latex or synthetic condom,
  - diaphragm, **or**
  - cervical cap

Contraception Warnings

Combined Oral Contraception

Due to the increased risk of venous thromboembolism in patients with multiple myeloma taking Lenalidomide S.K. in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking Lenalidomide S.K. monotherapy, combined oral contraceptive pills are not recommended, consider using ovulation inhibitory progesterone-only pills (i.e. desogestrel).
If a patient is currently using combined oral contraception the patient should switch to another effective method. 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 & IUDs

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

Females patients of childbearing potential must have a medically supervised negative pregnancy test (sensitivity of at least 25 mIU/mL):

- before starting the therapy, and once the patient had been using effective contraception for at least 4 weeks.
- At a monthly basis thereafter
- At dose interruptions
- 4 weeks following discontinuation

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.

A prescription for Lenalidomide S.K. for a female of childbearing potential must not be issued by the prescribing doctor until a negative pregnancy test has been verified by the prescribing doctor.

Pregnancy test results should be verified by the prescribing doctor prior to dispensing any prescription. This will be sent to K.S. Kim monthly using "Monthly Pregnancy Test Form"

Dispensing of Lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Pregnancy testing and counselling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. Lenalidomide S.K. therapy must be discontinued during this evaluation.

If pregnancy does occur during treatment, Lenalidomide S.K. must be discontinued immediately. Any suspected foetal exposure to Lenalidomide S.K. (during Lenalidomide therapy or within 4 weeks from stopping treatment) must be reported to the K.S. Kim immediately via the “Pregnancy Report Form.”

Refer the patient to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Men

In view of the expected teratogenic risk of Lenalidomide S.K., foetal exposure should be avoided.

Pharmacokinetic data has demonstrated that Lenalidomide is present in human semen.

As a precaution, all male patients taking Lenalidomide S.K. must meet the following conditions:

- The expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential, has been explained to him.
- If their partner is pregnant or of childbearing potential, male patients must use condoms throughout the duration of treatment, during dose interruption and for 4 weeks after cessation of treatment, **even if the male patient has undergone a vasectomy.**
- If pregnancy occurs in a partner of a male patient whilst he is taking Lenalidomide S.K. or shortly after he has stopped taking Lenalidomide S.K., he should inform his treating doctor immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice.

If Pregnancy Occurs/Side Effects

Stop treatment if pregnancy occurs during treatment with Lenalidomide S.K. Refer the patient (or patient's partner) to a physician specialised or experienced in teratology for evaluation and advice.

Notify K.S. Kim International Ltd. (K.S. Kim) & the Ministry of Health immediately of all such occurrences by using contact details below.

Please also complete "Pregnancy Report" included in this pack. K.S. Kim will wish to follow-up with you the progress of all pregnancies.

To the Ministry of Health

Use the portal of side effects reporting the Ministry of Health:

/https://sideeffects.health.gov.il/

To K.S. Kim International Ltd

- lenalidomide@sk-pharma.com
- 03-611-4543

Checklist for Prescribing doctors

☐ 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.

☐ **For male patients:** the patient was explained that he must use condoms during Lenalidomide therapy until 4 weeks after stopping therapy, even if they have undergone a successful vasectomy
When a male patient cannot use condoms: In the case of an allergy to latex or polyurethane, at least one highly effective form of contraception should be used by any female sexual partner.

☐ **For female patients** She must consistently and correctly use two highly effective method of contraception

- One highly effective form of contraception
  tubal ligation, IUD, hormonal (birth control pills, Injections, hormonal- patches, vaginal rings, or implants), or partner's vasectomy,
  and
- One additional effective contraceptive method
  male latex or synthetic condom, diaphragm, or cervical cap

☐ The patient, & when relevant the patient's female partner, were explained that the risk persists even after the medication is stopped and that they must not get pregnant within 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.

☐ The first prescription for Lenalidomide can only be given after the patient has had medically supervised pregnancy test and four weeks of contraceptive use. This is to make sure she is not already pregnant before starting treatment.

☐ The patient was explained that in order to support regular follow up, including pregnancy testing and monitoring, the prescription should be limited to 28 days.

☐ The patient was explained the need for and agrees to pregnancy testing before, during and after treatment.

☐ The patient was explained the need for periodic pregnancy tests with 28 days intervals throughout treatment and 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.

☐ 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.

☐ The patient has received a copy of the Patient Information Booklet.

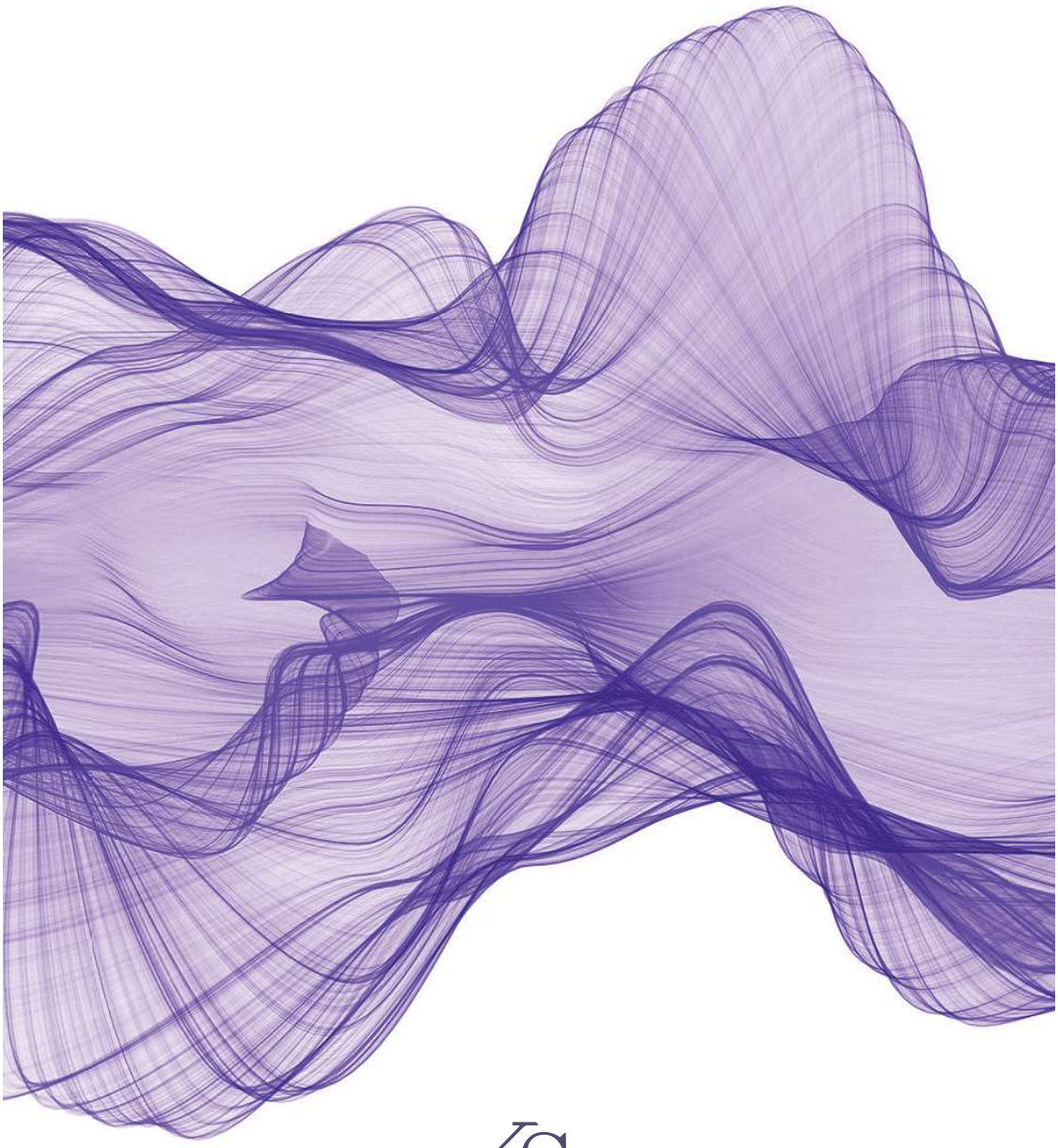
☐ The patient was explained that, according to Israeli ministry of health requirements, Lenalidomide S.K. is under controlled distribution program and that information regarding all patients and prescriptions is collected by K.S. Kim International. The information might be shared with the ministry of health and other applicable bodies, per regulatory requirements.

☐ The patient was explained 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.

☐ The patient was explained that Lenalidomide S.K. has been prescribed to her only and must not be shared with others.

☐ The patient was explained that they 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.



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