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LINADEX
PHYSICIAN EDUCATIONAL MATERIAL (PEM)

Embryo-Fetal Toxicity

Linadex (lenalidomide) is a thalidomide analogue and can cause serious birth defects or death to a developing baby. Hence, Linadex is contraindicated in pregnant women. It is also contraindicated in women of childbearing potential unless all the conditions of the Linadex Pregnancy Prevention Programme (PPP) are met.

LINADEX PPP (Pregnancy Prevention Program):

The PPP was developed to help healthcare professionals (HCPs) and patients understand the risks of Linadex (Lenalidomide) and pregnancy. This material provides a comprehensive overview of how the PPP prevents birth defects and exposure of lenalidomide to fetuses.

- Thalidomide is a powerful human teratogen and, if taken during pregnancy, can cause severe birth defects or death to a developing fetus. In the 1950s and 1960s, thalidomide was prescribed to pregnant women as a sedative and to relieve morning sickness. Consequently, approximately 12000 children were born with severe birth defects caused by thalidomide. Lenalidomide is structurally related to thalidomide. Lenalidomide induced malformations in monkeys similar to those described with thalidomide. If lenalidomide is given during pregnancy, a teratogenic effect in humans cannot be ruled out.
- Lenalidomide is contraindicated in pregnancy and in female patients of childbearing potential unless all of the conditions of the PPP, as described in this brochure, are met.
- Lenalidomide can pass into seminal fluid. Male patients must also follow the necessary requirements of the PPP to prevent exposure to a female partner.
- It is a requirement of the PPP that all HCPs ensure that they have read and understood this brochure before prescribing or dispensing lenalidomide to their patients.
- At treatment initiation, all male patients and all female patients of childbearing potential should undergo counseling about the need to avoid pregnancy. A counseling checklist (Healthcare Professionals Checklist for Counseling Patients Receiving Linadex Lenalidomide) is appended to this document to guide HCPs through the fulfillment of the PPP requirements. Please use the Patient Agreement Form for Linadex (Lenalidomide) to document patient understanding.
- Healthcare professionals are advised to refer to the Healthcare Professionals Checklist for Counseling Patients Receiving Linadex (Lenalidomide) for more information about ensuring that patients receiving treatment with lenalidomide are aware of the requirements of the PPP and the steps required for compliance.
- Patients should be capable of complying with the requirements for safe use of Linadex (Lenalidomide).
- Prior to treatment initiation, patients and HCPs must fill out and be provided with the Patient Agreement Form for Linadex (Lenalidomide) and Patient Medication Guide for Linadex (Lenalidomide). These materials will provide the relevant information to patients receiving treatment with lenalidomide.
- Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing, and prescriptions for all other patients can be for a maximum duration of 12 weeks.

For more information about prescribing and dispensing lenalidomide, including the recommended dosing schedule and duration, consult the Linadex® Package Insert.

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

Criteria for women of non-childbearing potential

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

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or during breast-feeding 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.

Linadex PPP Guidance for Female Patients of Childbearing Potential

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the conditions below:

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

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhoea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as Linadex is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

Contraception

Women of childbearing potential must use two effective methods of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after lenalidomide therapy and even in case of dose interruption 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 in order that contraception can be initiated.

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

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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 and dexamethasone, and to a lesser extent in patients with multiple myeloma 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 Linadex to women of childbearing potential should occur within 7 days of the prescription. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when Linadex 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 Linadex.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 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.

Linadex PPP Guidance for Male Patients

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 Linadex must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for at least 4 weeks after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Linadex or shortly after he has stopped taking Linadex, 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.

Additional precautions for all patients

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment for safe disposal.
- Patients should not donate blood during therapy or for at least 4 weeks following discontinuation of Linadex.
- Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule

Inform patients how to take Linadex capsules

- Linadex capsules should be taken once daily at about the same time each day,
- Linadex capsules may be taken either with or without food.
- The capsules should not be opened, broken, or chewed. Linadex capsules should be swallowed whole with water.
- Instruct patients that if they miss a dose of Linadex capsules, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take Linadex capsules at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Reporting Pregnancy

Healthcare providers and patients should report all cases of pregnancy to:
Hetero Labs Limited at + 656338 8036 and amreddy@hetero.com.sg

Reporting of Adverse Reactions

Local Country Contact Details
Hetero Labs Limited
Tel: +65 6338 8036

Email: amreddy@hetero.com.sg

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