HEALTHCARE PROFESSIONAL GUIDE TO LEAVDO RISK MANAGEMENT PROGRAM (RMP)

This guide provides key information about LEAVDO (Lenalidomide) and its Risk Management Program (RMP).
Due to its teratogenic risk, LEAVDO is available only through a restricted distribution system known as the LEAVDO RMP in Singapore. Only healthcare professionals (i.e., prescribers, pharmacists and nurses) enrolled under the LEAVDO RMP are eligible to prescribe/dispense LEAVDO. To receive LEAVDO, patients must enroll in the LEAVDO RMP and agree to adhere to its requirements. For more information, contact regulatory@pharmd.com.sg or +65 6837 2122.

INDICATIONS

LEAVDO is indicated for Multiple Myeloma:

- as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
- in combination with dexamethasone for the treatment of previously untreated multiple myeloma patients who are not eligible for transplant.
- in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

RISK OF TERATOGENICITY

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

An embryofetal development study indicated that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received lenalidomide at doses from 0.5-4 mg/kg/day during pregnancy. Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrioventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

LEAVDO RMP REQUIREMENTS

In view of the teratogenic risk associated with LEAVDO, fetal exposure should be avoided. LEAVDO is contraindicated in pregnancy, and in female patients of childbearing potential unless all of the conditions of the RMP are met. LEAVDO can pass into seminal fluid. Male patients must also follow the necessary requirements of the RMP to prevent exposure to a female partner.

Healthcare Professionals (HCP) must:

- Ensure that they have read and understood this guide
- Complete, sign and submit the HCP Letter of Undertaking (LOU) to regulatory@pharmd.com.sg prior to prescribing or dispensing LEAVDO to patients.
- Communicate the benefits and risks of treatment with LEAVDO to their patients
- Issue the Patient Guide to LEAVDO RMP to patients prior to treatment initiation
- Provide pregnancy prevention counseling as per patient risk categorization at treatment initiation, each consultation and each time a prescription is dispensed
- Ensure that the Patient Letter of Consent (LOC) is completed, signed and archived in the patient's medical records prior to initiation of LEAVDO therapy.
- Confirm a negative pregnancy test result prior to starting treatment and perform a pregnancy test prior to each prescription at every 4 weeks (if applicable)
- Issue prescriptions for women of childbearing potential for a maximum treatment duration of 4 weeks according to the approved indications and dosing regimens. Prescriptions for all other patients can be for a maximum duration of 12 weeks

Patients must:

- Receive and read the Patient Guide to LEAVDO RMP
- Understand and be capable of adhering to the requirements for safe use of LEAVDO

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- Complete, sign and submit the Patient Letter of Consent for LEAVDO RMP (LOC) to their prescriber prior to initiation of LEAVDO therapy

PATIENT GUIDANCE

Patients must be informed of the following:

- Do not donate blood during treatment (including during dose interruptions) and for at least 7 days after last dose
- Any unused medication at the end of treatment must be returned to pharmacy/ clinic for safe disposal
- Do not share the medicine with anyone else, even if they have similar symptoms
- Store the medicine away safely so that no one else can take the medicine by accident
- Keep the medicine out of reach of children

HANDLING PRECAUTIONS

- The capsules should not be opened, crushed or overly handled
- If powder content makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water
- If powder content makes contact with the mucous membranes, (moist inner lining of some body parts such as the nose and mouth), they should be thoroughly flushed with water
- HCP and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of. Hands should then be washed thoroughly with soap and water. **Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule**

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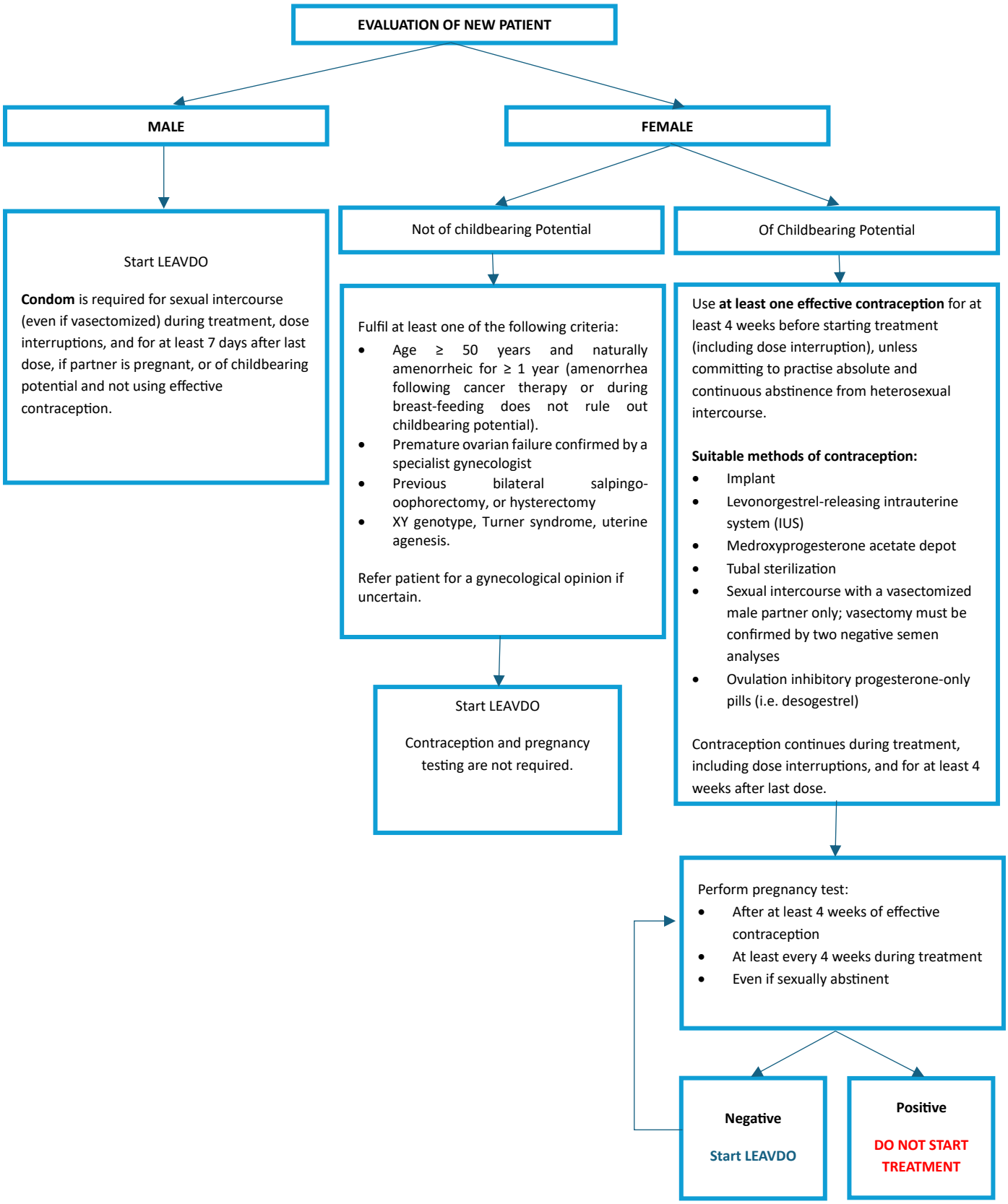
PATIENT RISK CATEGORIZATION, PREGNANCY TEST AND CONTRACEPTION REQUIREMENT ALGORITHM



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FEMALE PATIENTS OF CHILDBEARING POTENTIAL (even if they have amenorrhea or irregular menstrual periods) must:

- Use at least one effective contraception for at least 4 weeks before, during, and until at least 4 weeks after the last dose of treatment (including dose interruption) with LEAVDO
  OR
  Commit to absolute and continuous abstinence from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated by the HCP in relation to the treatment duration and the preferred and usual lifestyle of the patient. This should be confirmed and documented monthly by the HCP in the patient's medical records.
- Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25 mIU/mL) prior to starting treatment (during the consultation when LEAVDO is prescribed, or in the 3 days prior to the visit to the prescriber once the patient has been using effective contraception for at least 4 weeks), at least every 4 weeks during treatment (including dose interruptions), and at least 4 weeks after the last dose (unless confirmed tubal sterilization).
  **This includes female patients of childbearing potential who confirm absolute and continuous abstinence from heterosexual intercourse during the entire period of teratogenic risk associated with LEAVDO.*
- Be referred to a gynecologist for contraceptive advice if effective contraception is not established
- Inform all HCP involved in her care that she is on LEAVDO therapy
- Inform the treating doctor if a change or cessation in method of contraception is required
- Discontinue LEAVDO and inform the treating doctor immediately of a missed menstrual period, any unusual menstrual bleeding, or if she believes that she may be pregnant, or if a pregnancy does occur

Effective contraception methods include:

- Implant*
- Levonorgestrel-releasing intrauterine system*
- Medroxyprogesterone acetate depot
- Tubal sterilization
- Sexual intercourse with a vasectomized male partner only (vasectomy must be confirmed by two negative semen analyses)
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

**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.

Combined oral contraceptive (COC) pills are not recommended in view of increased risk of venous thromboembolism in multiple myeloma patients taking LEAVDO therapy. Patients should switch to one of the effective methods listed above if they are currently using COC. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing COC.

MALE PATIENTS must:

- Be informed about the risks and precautions associated with LEAVDO, including the potential risk of birth defects and the need for pregnancy prevention during and following treatment discontinuation.
- Not donate semen or sperm during treatment, including during dose interruptions and for at least 7 days following treatment discontinuation as LEAVDO can pass into seminal fluid.
- Use condoms throughout treatment duration, during dose interruptions, and for at least 7 days after cessation of treatment if his partner is pregnant or of childbearing potential and is not using effective contraception (even if the male patient has undergone vasectomy) as LEAVDO have been detected in seminal fluid.
- Inform his HCP immediately if his partner becomes pregnant while he is on treatment with LEAVDO within 7 days after medication has been discontinued. It is recommended that she be referred to a gynecologist specialized in teratology for evaluation and advice.

Effective contraceptive methods his female partner can use include implant, levonorgestrel-releasing intrauterine system, medroxyprogesterone acetate depot, tubal sterilization, sexual intercourse with a vasectomized male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation, inhibitory progesterone-only pill (i.e. desogestrel).

IN THE EVENT OF A SUSPECTED PREGNANCY OR EXPOSURE OF A PREGNANT PARTNER
Female patient

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Stop treatment immediately and inform the treating HCP immediately. Refer the patient to a HCP specialised or experienced in teratology for evaluation and advice.

Male patient
Inform the treating HCP immediately if the female partner becomes pregnant while he is on treatment with LEAVDO, or within 7 days after last dose. Refer the female partner to a HCP specialised or experienced in teratology for evaluation and advice.

OTHER RISKS ASSOCIATED WITH LEAVDO

1. **Thrombocytopenia**
   - Monitor complete blood counts, including platelet count at baseline, weekly during first 8 weeks and monthly thereafter
   - Monitor for signs of bleeding (epistaxis) especially with concomitant use of medications known to increase bleeding risk
   - Management may require dose adjustment, blood product support and/or growth factors
   - Refer to LEAVDO package insert on the recommended dose modifications during treatment and restart of treatment after an episode of thrombocytopenia

2. **Second primary malignancies (SPM)**
   - Risk of occurrence must be considered before treatment initiation
   - Carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated

3. **Tumor flare reaction and Tumor lysis syndrome**
   - Risk factors include patients with high tumor burden prior to treatment
   - Monitor closely and take appropriate precautions when necessary

ADVERSE EVENT/ REACTION REPORTING

Please report any adverse reactions to Pharm-D via:
- Email: Regulatory@pharmd.com.sg
- Phone: +65-6837 2122

You are also encouraged to report any suspected adverse reactions to the Vigilance & Compliance Branch, Health Products Regulation Group, Health Sciences Authority at https://www.hsa.gov.sg/adverse-events

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