Healthcare Professional Brochure

Revlimid

Introduction

- Revlimid is an immunomodulating medicinal product. In Phase III clinical studies, Revlimid in combination with high-dose dexamethasone prolonged median time to progression (TTP) by about at least 28 weeks compared with dexamethasone alone in patients who have received at least one prior therapy for multiple myeloma.

- Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy

- Revlimid is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4mg/kg/day. Findings from this study showed that lenalidomide produced malformations (short limbs, bent fingers/toes, wrist and/or tail, supernumerary or absent fingers/toes) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study. If Revlimid is taken during pregnancy, a teratogenic effect can be expected. Therefore Revlimid is contraindicated in pregnancy and in women of child bearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) described in this brochure are carried out.

- All men and all women of childbearing potential should undergo counselling of the need to avoid pregnancy. Treatment Initiation Forms are provided for this purpose with this Kit. These forms should be signed by both physician and patient; one copy retained by the patient and the other being retained in the patients records

- Patients should be capable of complying with the requirements of safe use of Revlimid

- Patients must be provided with appropriate patient educational brochure and a copy of the Treatment Initiation Form.

- Lenalidomide is only approved for use with dexamethasone for the treatment of multiple myeloma for patients who have received at least one prior therapy. Other indications are under investigation but the dosing and safety profile may differ.

- This document sets out the key points relating to the safe use of Revlimid. For further information, please see the enclosed Summary of Product Characteristics.

Safety Advice relevant to all patients
Myelosuppression

- Neutropenia and thrombocytopenia are the major dose limiting toxicities

- The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with an incidence of grade 4 neutropenia of 5.1%. Grade 4 febrile neutropenia episodes were observed infrequently in 0.6% in lenalidomide/dexamethasone-treated patients.

- The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia 9.9% and 1.4%, respectively.

- A complete blood count, including white blood count monitoring with differential count, platelet count, haemoglobin and haematocrit should be performed at baseline and every week for the first 8 weeks of treatment and then monthly thereafter.

- Revlimid treatment must not be started if the Absolute Neutrophil Counts (ANC) $<1.0 \times 10^9$/l, and/or platelet count$<75 \times 10^9$/l or, dependent on bone marrow infiltration by plasma cells, platelet counts $<30 \times 10^9$/l .

Recommended dosage adjustments during treatment and restart of treatment
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to Revlimid.

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 $< 30 \times 10^9$/l	Interrupt Revlimid treatment
Return to $\geq 30 \times 10^9$/l	Resume Revlimid at Dose Level 1
For each subsequent drop below 30×10^9/l	Interrupt Revlimid treatment
Return to $\geq 30 \times 10^9$/l	Resume Revlimid 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 10^9/l	Interrupt Revlimid treatment
Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	Resume Revlimid at Starting Dose once daily
Return to ≥ 0.5 x 10^9/l when dose-dependent haematological toxicities other than neutropenia are observed	Resume Revlimid at Dose Level 1 once daily
For each subsequent drop below < 0.5 x 10^9/l	Interrupt Revlimid treatment
Return to ≥ 0.5 x 10^9/l	Resume Revlimid at next lower dose level (Dose Level 1, 2 or 3) once daily. Do not dose below 5 mg once daily.

- In case of neutropenia, the physician should consider the use of growth factors in patient management.

Venous and arterial thromboembolism

- The combination of Revlimid and dexamethasone is associated with an increased risk of venous and arterial thromboembolic events (mainly deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarctions and cerebrovascular events) in patients with multiple myeloma.

- In clinical trials there was a significantly increased risk for developing thromboembolic adverse events (deep vein thrombosis, pulmonary embolism) in lenalidomide/dexamethasone-treated patients compared with placebo/dexamethasone–treated patients (9.1% versus 4.3% and 4.0% versus 0.9%, respectively).

- Action should be taken to try to minimize all modifiable risk factors for thromboembolic events (e.g. smoking cessation, control of hypertension and hyperlipidaemia). Patients with known risk factors for thromboembolism including previous thrombosis should be closely monitored.

- Several risk factors have been identified which may increase the risk of thrombo-embolism in patients being treated with Revlimid and dexamethasone. These include concomitant administration of erythropoietic agents or previous history of DVT.

- Prophylactic antithrombotic medications, such as low molecular weight heparins or warfarin are recommended especially in patients with additional thrombotic

risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

- If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Initial dosing in patients with renal failure

- Revlimid 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. The following dosage adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

Renal Function (CLcr)	**Dose Adjustment**
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	15 mg every other day**
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5mg once daily. On dialysis days, the dose should be administered following dialysis.

*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.

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

Thyroid function

Cases of hypothyroidism have been reported and monitoring of thyroid function should be considered.

Peripheral neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.

Tumour Lysis Syndrome

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Allergic Reactions

Cases of allergic reaction/hypersensitivity reactions have been reported. Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe Skin Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Use in patients with impaired hepatic function

- Revlimid has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Disposal of unwanted medicine

- Patients should be advised never to give Revlimid to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Blood donation

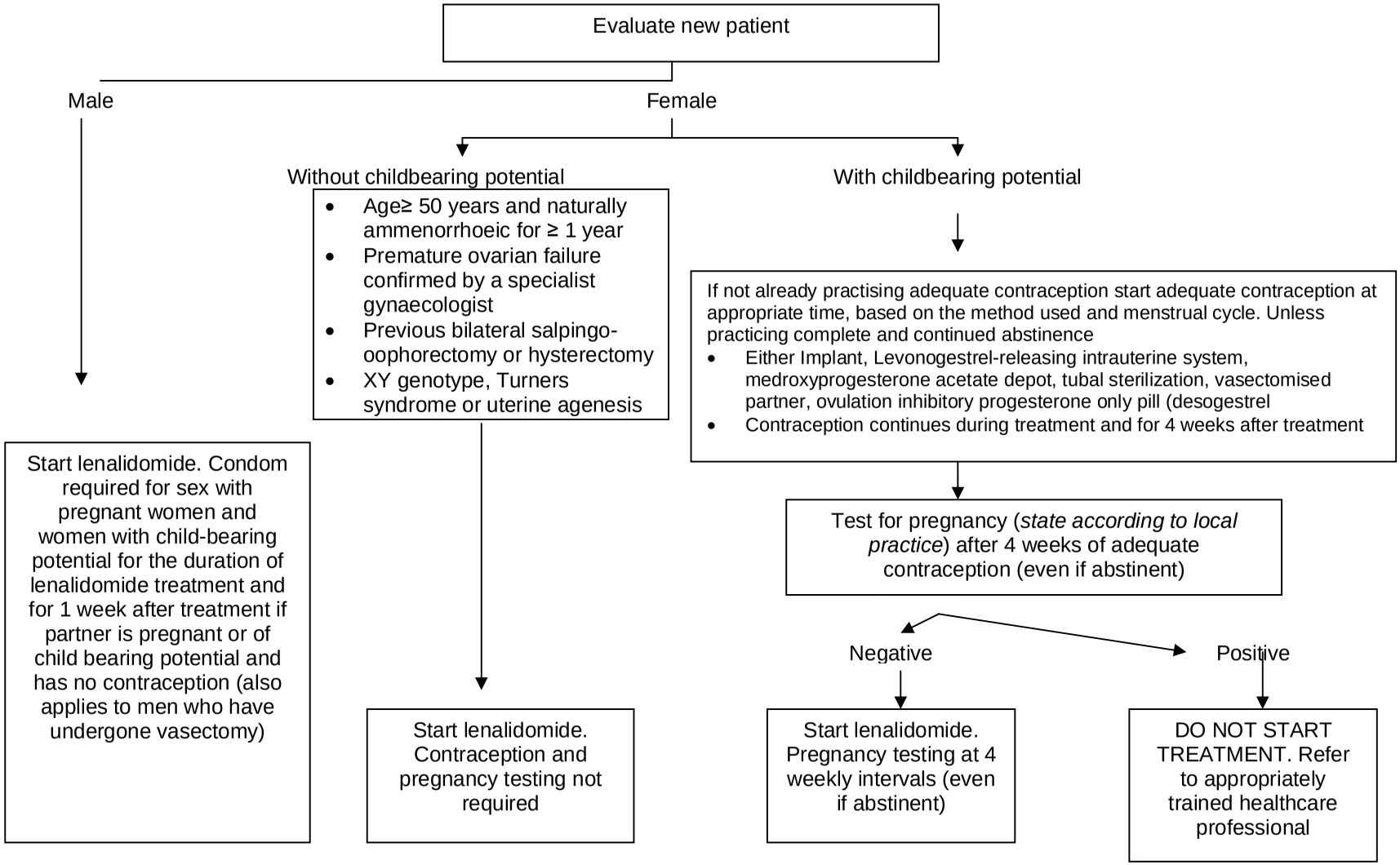
Patients should not donate blood during treatment and for one week after cessation of treatment with Revlimid.

Pregnancy Prevention Programme

- Revlimid is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance. Revlimid induced malformations in monkeys similar to those described for thalidomide. If Revlimid is taken in pregnancy, a teratogenic effect in humans is expected.

- Revlimid is therefore contraindicated in pregnancy. It is also contraindicated in women of childbearing potential unless all the conditions of the Revlimid Pregnancy Prevention Programme are met.

- The Pregnancy Prevention Programme is set out in the following Algorithm



- The following are considered to not have childbearing potential.
    - Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
    - Confirmed premature ovarian failure if confirmed by specialist gynaecologist.
    - Previous bilateral salpingo-oophorectomy, or hysterectomy
    - XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

You are advised to refer your patient for a gynaecological opinion if you are unsure whether or not she meets these criteria.

Safety Advice for Women of Child Bearing Potential

- In view of the expected teratogenic risk of Revlimid, foetal exposure should be avoided

- Women of childbearing potential (even if they have amenorrhoea) must:
    - use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after Revlimid therapy, and even in case of dose interruption.
    - commit to absolute and continuous abstinence

    AND
    - Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25m IU/ml) once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy and 4 weeks after the end of therapy (unless confirmed tubal sterilisation). This includes those women of childbearing potential who confirm absolute and continuous abstinence.

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)

- Your patient should be advised that if a pregnancy does occur whilst she is receiving Revlimid, she must stop treatment immediately and inform her physician immediately.

Safety Advice for Men

- In view of the expected teratogenic risk of Revlimid, foetal exposure should be avoided

- Revlimid is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for one week after cessation of treatment if their partner is pregnant or of child bearing potential and has no contraception and even if the male patient has undergone vasectomy.

- Patients should be instructed that if their partner becomes pregnant whilst he is taking Revlimid or shortly he has stopped taking Revlimid 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.

Requirements in the event of a pregnancy

- Stop treatment
- Refer patient to a physician specialised or experienced in teratology for evaluation and advice.
- Notify Celgene of all such occurrences. (see below for contact details)
    - Pregnancy Capture Form is included in this pack
    - Celgene will wish to follow-up with you the progress of all pregnancies.

Reporting of Adverse Reactions

- Physicians, pharmacists, and other specialised healthcare professionals should report all adverse drug reactions to Celgene An Adverse Reaction Report form is provided in this pack.
- Such reports of adverse events and pregnancies should also be reported to:

Drug Safety Europe, Celgene

Tel : +41 32 723 8476.

Fax : +41327 298 409

Email : drugsafetyeurope@celgene.com

Communication of Safety Information to other Physicians

It is important that other physicians, for example the patient's general practitioner, who may care for the patient for other conditions are aware of the potential risks of lenalidomide. To assist in this communication, the CD ROM included in this pack includes a template containing the key safety information for lenalidomide. This wording can be copied and pasted as required into communications and between you and other physicians involved in the patient care.

Distribution mechanism for lenalidomide supply

Celgene has implemented a controlled distribution system in order to ensure prevention of foetal exposure to lenalidomide. Prior to treating a patient with lenalidomide, it is required that the treating physician and the patient sign a Treatment Initiation Form to confirm that the benefits and risks of lenalidomide therapy have been explained and understood and that the requirements of the Pregnancy Prevention Programme will be complied with. One copy of this form should be given to the patient and the other should be retained in the patient file. In addition, patients should be provided with the relevant patient information booklet in Maltese or English.

Patient Cards to document childbearing status are contained within the Healthcare Professional Kit. The Patient Cards must be signed to confirm counselling has taken place. For women of childbearing potential, the Patient Card will also document the date and results of the monthly pregnancy test.. The Patient Card must be completed and a copy provided to the patient. The pharmacist will be required to verify the correct completion of the patient card for each female patient prior to each dispense of lenalidomide.

For those patients who are women of childbearing potential, prescriptions should be limited to one month supply. Dispensing of lenalidomide to women of childbearing potential should only occur within a maximum of 7 days of either the prescription date or the last pregnancy test date, whichever comes first.