Revlimid®

Information for Healthcare Professionals

Brochure

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. In a Phase III clinical study (MDS-004), a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

- Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy
  AND
- Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

- 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 digits, wrist and/or tail, supernumerary or absent digits) 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 described in this brochure are carried out.

- All men and all women of childbearing potential should undergo counselling of the need to avoid pregnancy (checklists for counselling are provided with this pack)

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

- Patients must be provided with appropriate patient educational brochure and patient card

- Local country specific arrangements about enrolment of patients with MDS in the MDS PASS according to the national implementation of the MDS PASS as agreed on by the National Competent Authority.

Safety Advice relevant to all patients

1. 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% compared with 0.6% in placebo/dexamethasone-treated patients.. Grade 4 febrile neutropenia episodes were observed infrequently in 0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/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, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients)

- In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% of patients on placebo. Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

- 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 to monitor for cytopenias. A dose reduction may be required. In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution

1.1 Multiple Myeloma

- 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 .

- The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing

is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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

Thrombocytopenia

When platelets	Recommended Course
First fall to < 30 x 10^9/l Return to ≥ 30 x 10^9/l	Interrupt Revlimid treatment Resume Revlimid at Dose Level -1
For each subsequent drop below 30 x 10^9/l Return to ≥ 30 x 10^9/l	Interrupt Revlimid treatment Resume Revlimid at next lower dose level (Dose Level -2 or -3) once daily. Do not dose below 5 mg once daily.

Neutropenia

When neutrophils	Recommended Course
First fall to < 0.5 x 10^9/l Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	Interrupt Revlimid treatment 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 Return to ≥ 0.5 x 10^9/l	Interrupt Revlimid treatment 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.

1.2 Myelodysplastic Syndromes

- Revlimid treatment must not be started if the Absolute Neutrophil Count (ANC) < 0.5 x 10^9/l and/or platelet count < 25 x 10^9/l.

- The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings

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

- *Dose reduction steps*

Starting Dose	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days
Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

Thrombocytopenia

When platelets	Recommended Course
Fall to < 25 x 10^9/l Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

Neutropenia

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l Return to ≥ 0.5 x 10^9/l	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

For patients who experience other toxicities

For other grade 3 or 4 toxicities judged to be related to lenalidomide, stop treatment and restart 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 or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Safety Advice relevant to all patients

2. **Venous and arterial thromboembolism**

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

In patients with myelodysplatic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma

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- 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.

- Concomitant administration of erythropoietic agents or previous history of DVT may also increase the thrombotic risk in these patients.

- 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.

3. 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.

3.1 Multiple myeloma

Renal Function (CLcr)	**Dose Adjustment** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5mg once daily. On dialysis days, the dose should be administered following dialysis.

[1]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.
[2] In countries where the 7.5 mg capsule is available.
[3] The dose may be escalated to 10mg once daily if the patient is tolerating the treatment.

3.2 Myelodysplastic syndromes

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)

Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

4. Thyroid function

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

5. 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.

6. 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.

7. 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.

8. 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.

9. Second primary malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of SPM has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated

10. Progression to acute myeloid leukaemia in low- and int-1-risk MDS

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in patients who are transfusion dependent and have a Del (5q) abnormality. The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

11. <u>Use in patients with impaired hepatic function</u>

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

12. <u>Disposal of unwanted medicine</u>

- 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.

13. Blood donation

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

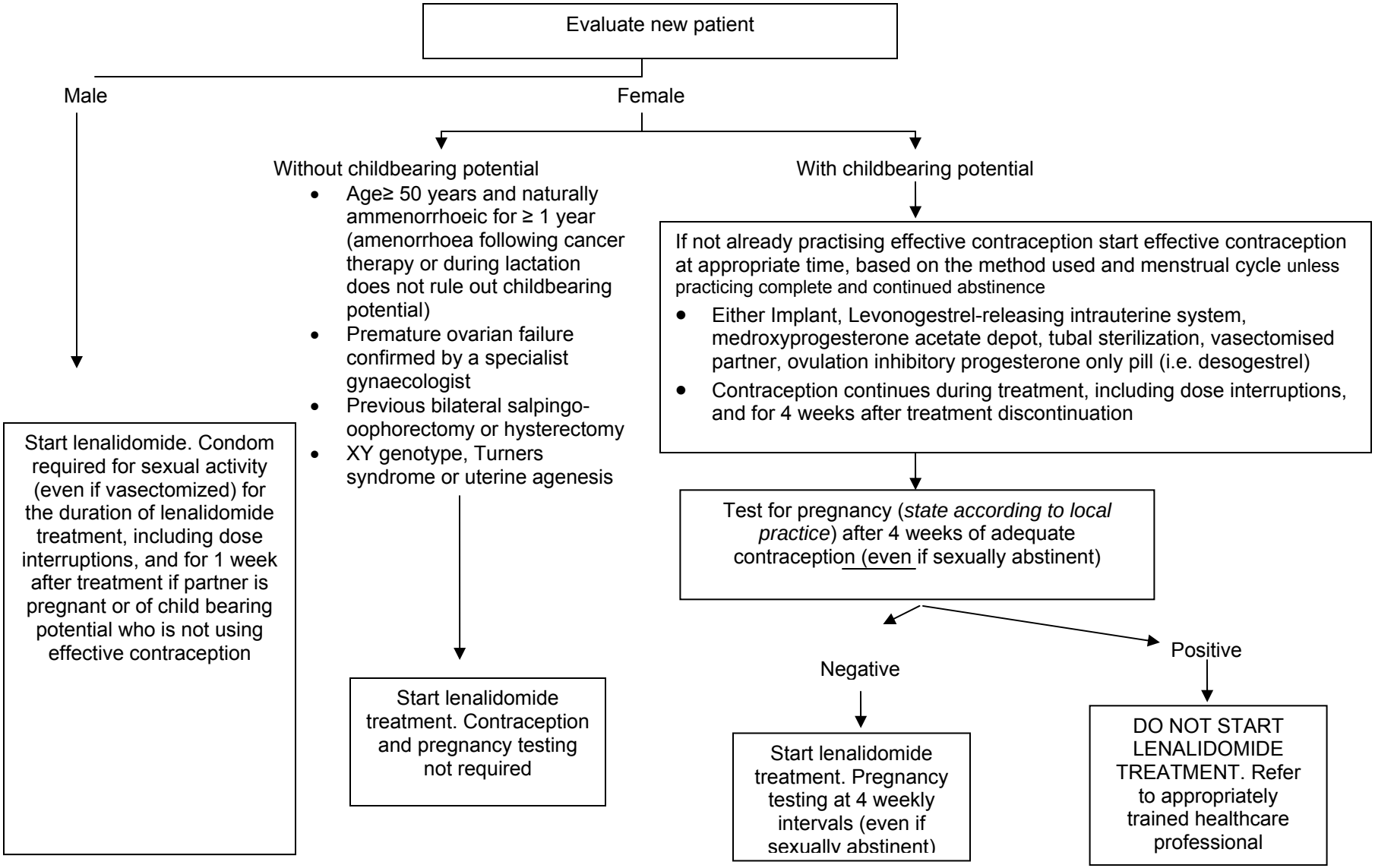
Local country specific arrangements for a prescription of Revlimid to be dispensed i.e. local description of local PPP requirements Include dispensing to women of childbearing potential should occur within a maximum of 7 days from the prescription.

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 or during lactation 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 Childbearing Potential

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

- Women of childbearing potential (even if they have ammenorrhoea) 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 or
    - commit to absolute and continuous sexual abstinence

    AND
    - Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25 mIU/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 continued sexual abstinence *Add here available tests according to local practice*

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 who is not using effective 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.
    - Pregnancy Capture Form is included in this pack
    - *Add local contact details of local Celgene Office*
    - Celgene will wish to follow-up with you the progress of all pregnancies.
- *Add, as appropriate, local requirements to report to local Regulatory Agency in accordance with local regulations*

Reporting of Adverse Reactions

The safe use of Revlimid is of paramount importance. As part of Celgene's ongoing safety monitoring, the company wishes to learn of Adverse Reactions that have occurred during the use of Revlimid. Adverse Reaction report forms are included in this Health Care Professional Kit. *Add local contact details of local Celgene office and where to report Adverse Reactions in accordance with the local Regulatory requirements of individual countries.*

Enclosures

- Checklists
- Pregnancy Reporting Form with local contact details
- Patient Card
- Patient brochure
- Local country specific details on the MDS PASS emphasizing that prior to prescribing Revlimid, the healthcare professionals should enroll the MDS patients into the PASS according to the national implementation of the MDS PASS as agreed on by the National Competent Authority