SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

REVLIMID® 5 mg Hard capsules

REVLIMID® 10 mg Hard capsules

REVLIMID® 15 mg Hard capsules

REVLIMID® 25 mg Hard capsules

COMPOSITION:

Each Revlimid 5 mg hard capsule contains 5 mg of lenalidomide

Each Revlimid 10 mg hard capsule contains 10 mg of lenalidomide

Each Revlimid 15 mg hard capsule contains 15 mg of lenalidomide

Each Revlimid 25 mg hard capsule contains 25 mg of lenalidomide

LIST OF EXCIPIENTS:

Lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

The 5 mg and 25 mg capsule shells contain gelatin, titanium dioxide (E171) and black ink*.

The 10 mg capsule shells contain gelatin, FD&C blue #2 (indigo carmine; E132), yellow iron oxide (E172), titanium dioxide (E171) and black ink*.

The 15 mg capsule shell contains gelatin, FD&C blue #2 (indigo carmine; E132), titanium dioxide (E171) and black ink*.

* Black ink contains shellac, black iron oxide (E172) and potassium hydroxide.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION

A32 Other – Immunomodulators

WARNING: SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS.

Lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see 'Pregnancy and lactation'). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FOETAL EXPOSURE TO REVLIMID AS NEGLIGIBLE AS POSSIBLE, REVLIMID IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE KEY ASSIST RISK MANAGEMENT PROGRAM.

UNDER THIS RESTRICTED DISTRIBUTION PROGRAMME, ONLY PRECRIBERS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO PRESCRIBE THE PRODUCT AND PHARMACISTS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE KEY ASSIST RISK MANAGEMENT PROGRAM.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lenalidomide is an oral immunomodulating agent with a pleiotropic mechanism of action involving direct tumouricidal activity, immunomodulation, pro-erythropoiesis, and anti-angiogenesis. Lenalidomide inhibits proliferation of certain haematopoietic

tumour cells (including multiple myeloma plasma tumour cells and those with deletions of chromosome 5) and induces expression of tumour suppressor genes, leading to cell cycle arrest. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NK T cells, and inhibition of proinflammatory cytokines (e.g. TNF-α and IL-6) by monocytes. Pro-erythropoietic properties of lenalidomide include expansion of CD34+ haematopoietic stem cells and increased foetal haemoglobin production. In multiple myeloma cells, the combination of lenalidomide and dexamethasone induces expression of tumour suppressor genes, activates caspases involved in apoptosis, and synergistically inhibits MM cell proliferation.

In myeloplastic syndromes (MDS) (del 5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing apoptosis of del 5q cells. Sensitivity to lenalidomide in MDS del (5q) can, at least in part, be explained by upregulation of genes (e.g. SPARC, p21, RPS14) which have reduced expression due to haploinsufficiency caused by del (5q).

Cardiac Electrophysiology

A QTc study was conducted to evaluate the effects of lenalidomide on QT interval at single doses of 10 mg and 50 mg. A single dose of lenalidomide up to 50 mg is not associated with prolongation of the QT interval in healthy male subjects.

Pharmacokinetic properties:

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with the maximum plasma concentration (C_{max}) occurring between 0,5 and 1,5 hours

post dose. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionally with increases in dose. Multiple dosing at the recommended dose-regimen does not result in lenalidomide accumulation.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20 % decrease in area under the concentration versus time curve (AUC) and 50 % decrease in C_{max} in plasma. In the pivotal multiple myeloma and MDS registration trials where the efficacy and safety were investigated for lenalidomide, it was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

In multiple myeloma patients (baseline serum creatinine level ≤ 1,5 mg/dl), C_{max} occurs between 0,5 to 6 hours postdose. Plasma exposure (AUC and C_{max}) increases proportionally with dose following single and multiple doses. Multiple doses at 25 mg/day do not cause lenalidomide to accumulate in plasma. Exposure (AUC) in multiple myeloma patients is higher compared to healthy volunteers since lenalidomide clearance is lower in these patients than in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients (dose adjustments are recommended for patients with CLcr < 60 ml/min; see 'dosage and directions for use' and 'use in patients with impaired renal function').

In patients with low - or intermediate-1-risk MDS, a single 10 mg oral dose of lenalidomide is rapidly absorbed with the C_{max} observed at around 1 hour postdose. There is no accumulation of lenalidomide in plasma with multiple doses at 10 mg per day. Because many MDS patients have some degree of renal impairment, the exposure (AUC) is higher in MDS patients as compared with healthy subjects (dose

adjustments are recommended for patients with CLcr < 60 ml/min; see ‘dosage and directions for use’ and ‘use in patients with impaired renal function’).

Distribution:

In vitro [^{14}C]-lenalidomide binding to plasma proteins is approximately 29 % in healthy volunteers and 23 % in multiple myeloma patients.

Lenalidomide is present in semen (< 0,01 % of the dose) after administration of 25 mg/day and the substance is undetectable in semen 3 days after discontinuation of lenalidomide.

Metabolism:

Lenalidomide is not a substrate of hepatic metabolic enzymes *in vitro*. Unchanged lenalidomide is the predominant circulating component *in vivo* in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitute less than 5 % of parent levels in circulation.

Excretion:

Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy volunteers, approximately 90 % and 4 % of the radioactive dose is eliminated in urine and faeces, respectively. Approximately 82 % of the radioactive dose is excreted as lenalidomide, almost exclusively via the urinary route. Hydroxy-lenalidomide and Nacetyl-lenalidomide represent 4,59 % and 1,83 % of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

In MDS patients, urinary excretion of unchanged lenalidomide in 24 hours post-dose averages approximately 65 % of the administered dose.

At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and ranged from 3 to 5 hours in patients with multiple myeloma or MDS.

Pharmacokinetics in children:

No data are available.

Pharmacokinetics in the elderly:

No data are available.

Pharmacokinetics in renal Impairment:

The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant conditions. In this study, 5 patients with mild renal function impairment (creatinine clearance (CLcr) 56-74 ml/min), 6 patients with moderate renal function impairment (CLcr 33-46 ml/min), 6 patients with severe renal function impairment (CLcr 17-29 ml/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25 mg dose of lenalidomide. Seven (7) healthy subjects of similar age with normal renal function (CLcr 83-145 ml/min) were administered a single oral 25 mg dose of lenalidomide. The pharmacokinetics of lenalidomide were similar in patients with mild impairment CLcr 56-74 ml/min and healthy subjects. Moderately and severely impaired patients had a 3-fold increase in half-life and a 66 % to 75 % decrease in clearance compared to healthy subjects. Patients on haemodialysis had an approximately 4,5-fold increase in half-life and an 80 % decrease in clearance compared to healthy subjects. Approximately 30 % of the substance in the body was removed by a 4-hour dialysis session.

Pharmacokinetics in hepatic impairment:

No data are available.

INDICATIONS:

Myelodysplastic Syndromes (MDS):

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

Multiple Myeloma:

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

CONTRA-INDICATIONS :

- Pregnancy and lactation.
- Women of childbearing potential, except when all of the conditions for pregnancy prevention have been met (see 'Pregnancy and lactation' and 'Warnings and special precautions').
- Hypersensitivity to lenalidomide or any of the excipients.

WARNINGS AND SPECIAL PRECAUTIONS:

General:

Pregnancy warning

Revlimid is contra-indicated during pregnancy.

Revlimid 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 (see ‘pregnancy and lactation’). If Revlimid is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Key Assist Risk Management Program must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Counselling

For women of childbearing potential, Revlimid 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, 4 weeks before starting treatment, throughout the entire duration of treatment including dose interruptions, and for 4 weeks after the end of treatment.
- Even if a woman of childbearing potential has amenorrhea 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 Revlimid is dispensed following a negative pregnancy test.
- She understands the need and accepts to undergo pregnancy testing 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 Revlimid.

For male patients taking Revlimid, 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 discontinuation of lenalidomide in the healthy subject (see 'pharmacokinetics'). As a precaution, all male patients taking

Revlimid must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a woman of childbearing potential.
- Understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Key Assist Risk Management Program, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use two reliable methods of contraception for 4 weeks before therapy, during therapy including dose interruptions, and until 4 weeks after Revlimid therapy 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 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:

Highly effective methods

- Intra Uterine Device (IUD);

- Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS)), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills (e.g. desogestrel);
- Tubal ligation;
- Partner's vasectomy.

Effective methods

- Male condom;
- Diaphragm;
- Cervical cap.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking Revlimid and dexamethasone, and in patients with myelodysplastic syndromes taking Revlimid monotherapy, combined oral contraceptive pills are not recommended (see also 'Interactions'). If a patient is currently using combined oral contraception the patient should switch to two of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.

Pregnancy testing

Pregnancy must be excluded by testing blood and/or urine.
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 50 IU/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 Revlimid to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment

A medically supervised pregnancy test should be performed 7 days prior to the patient starting Revlimid 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 Revlimid.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 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 7 days prior to the visit to the prescriber.

Male fertility

Revlimid is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of Revlimid in the healthy subject (see 'Pharmacokinetics'). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is of childbearing potential and is not established on suitable contraception (even if the male patient has undergone a vasectomy). Male patients taking Revlimid should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the end of treatment.

Patients should not donate blood during therapy including dose interruptions and for

4 weeks following discontinuation of Revlimid.

Educational materials

In order to assist patients in avoiding foetal exposure to Revlimid, educational material will be provided to health care professionals to reinforce the warnings about the expected teratogenicity of Revlimid, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. Full patient information about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Key Assist Risk Management Program should be given by the medical practitioner to women of childbearing potential and, as appropriate, to male patients.

Other special warnings and precautions for use:

- *Venous thromboembolic events* (predominantly deep venous thrombosis and pulmonary embolism), in multiple myeloma patients treated with Revlimid combination therapy and in MDS patients treated with Revlimid monotherapy.
- *Allergic Conditions*: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive Revlimid. Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash. Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions.
- *Tumour Lysis Syndrome and Tumour Flare Reaction*

Tumour lysis syndrome (TLS) and tumour flare reaction (TFR) have been observed in patients with CLL, and in patients with other lymphomas, who were treated with Revlimid. Fatal instances of TLS have been reported during treatment with Revlimid. Patients at risk for TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to Revlimid. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been reports of TLS in patients with MM treated with Revlimid.

Myelodysplastic syndromes (MDS):

Haematologic toxicity (neutropenia and thrombocytopenia) in deletion 5q MDS – A complete blood cell count, including white blood cell count with differential, platelet count, haemoglobin, and haematocrit should be performed weekly for first 8 weeks of Revlimid treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see 'Dosage and directions for use').

Multiple myeloma:

Haematological toxicities:

- Previously treated MM:

Haematologic toxicity (neutropenia and thrombocytopenia) in previously treated multiple myeloma patients treated with Revlimid combination therapy – Complete blood cell counts should be monitored every 2 weeks for the first 12 weeks and then monthly thereafter. A dose interruption and/or dose reductions may be required (see 'Dosage and directions for use').

Second Primary Malignancies

- Previously treated MM

A numerical imbalance was observed in clinical trials in previously treated multiple myeloma patients with Revlimid/dexamethasone compared with controls comprising invasive primary malignancies and of basal cell and squamous cell skin cancers Carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

Effects on ability to drive vehicles and operate machinery:

No studies on the effects on the ability to drive or use machines have been performed. Revlimid may affect the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of Revlimid. Therefore, caution is recommended when driving or operating machines.

Lactose intolerance: Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Revlimid. Risk-benefit of Revlimid treatment should be evaluated in patients with lactose intolerance.

INTERACTIONS:

Lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes *in vitro*. Hence, co-administration of cytochrome P450 substrates or inhibitors with Revlimid is not likely to result in clinically relevant medicine interactions.

Co-administration of multiple doses of 10 mg of Revlimid had no effect on the single dose pharmacokinetics and pharmacodynamic of R- and S-warfarin.
Coadministration of a single 25 mg dose of warfarin had no effect on the

pharmacokinetics of Revlimid. It is not known whether there is an interaction during concomitant treatment with dexamethasone. Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

When digoxin was co-administered with Revlimid (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were 14 % higher than when digoxin was administered concomitantly with placebo. Periodic monitoring of digoxin plasma levels is recommended during administration of Revlimid.

In patients with multiple myeloma, co-administration of single or multiple doses of dexamethasone (40 mg/day) had no significant effect on the multiple dose pharmacokinetics of Revlimid (25 mg/day).

In vitro, Revlimid is a weak substrate, but is not an inhibitor of P-glycoprotein (P-gp).

In vitro studies demonstrate that Revlimid is not a substrate of human multidrug resistance protein MRP1, MRP2 or MRP3 efflux transporters as well as human organic anion and cation uptake transporters OAT1, OAT3, OATP1B1 (OATP2) or OCT1.

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving Revlimid with dexamethasone
(see 'Warnings and Special precautions' and 'Side effects).

Patients with multiple myeloma taking Revlimid and dexamethasone, patients with MDS taking Revlimid monotherapy, as well as patients taking combined oral contraceptive pills or hormone replacement therapy, have an increased risk of venous thromboembolic events (VTE).

PREGNANCY AND LACTATION:

Revlimid is contraindicated in females who are pregnant or who could become pregnant.

Pregnancy:

Revlimid is teratogenic to animals. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore:

- Females of childbearing potential must use effective means of contraception for 28 days before therapy, during Revlimid therapy including dose interruptions, and for 28 days following discontinuation of Revlimid therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with multiple myeloma taking Revlimid and dexamethasone, and in patients with MDS taking Revlimid monotherapy, and an increased risk of VTE in patients taking combined oral contraceptive pills.
- Females of childbearing potential should undergo regular pregnancy testing during treatment with Revlimid.
- If pregnancy does occur during treatment, Revlimid should be immediately discontinued.

Males:

- Clinical data has demonstrated the presence of lenalidomide in human semen. Therefore, male patients taking Revlimid should use a condom during Revlimid therapy including dose interruptions and for 4 weeks after cessation of treatment. Male patients taking Revlimid should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the discontinuation of treatment.

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*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

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

Lactation:

Breastfeeding is contra-indicated during therapy with Revlimid.

DOSAGE AND DIRECTIONS FOR USE:

Administration

Revlimid should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. Revlimid capsules should be swallowed whole, preferably with water, either with or without food.

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. Do not take 2 doses at the same time.

Myelodysplastic syndromes (MDS):

Recommended dosage:

The recommended starting dose of Revlimid is 10 mg given orally once a day on days 1-21 of repeating 28-day treatment cycles.

Recommended dose adjustments during treatment and restart of treatment**:**

Platelet counts

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg

If baseline ≥ 100 x 10^9/l	
When Platelets	Recommended Course
Fall to < 50 x 10^9/l	Interrupt Revlimid treatment
Return to ≥ 50 x 10^9/l	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles
If baseline < 100 x 10^9/l	
When Platelets	Recommended Course
Fall to 50 % of the baseline value	Interrupt Revlimid treatment
If baseline ≥ 60 x 10^9/l and returns to ≥ 50 x 10^9/l	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles
If baseline < 60 x 10^9/l and returns to ≥ 30 x 10^9/l	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg

When Platelets	Recommended Course
< 30 x 10^9/l or < 50 x 10^9/l with platelet transfusions	Interrupt Revlimid treatment

Return to ≥ 30 x 10^9/l (without signs of bleeding)	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily

When Platelets	Recommended Course
< 30 x 10^9/l or < 50 x 10^9/l with platelet transfusions	Interrupt Revlimid treatment
Return to ≥ 30 x 10^9/l (without signs of bleeding)	Resume Revlimid at 5 mg every other day

Neutrophil counts (ANC)+

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg

If baseline ANC ≥ 1 x 10^9/l	
When Neutrophils	Recommended Course
Fall to < 0,75 x 10^9/l	Interrupt Revlimid treatment
Return to ≥ 1 x 10^9/l	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles

If baseline ANC < 1 x 10^9/l	
When Neutrophils	Recommended Course
Fall to < 0,5 x 10^9/l	Interrupt Revlimid treatment
Return to ≥ 0,5 x 10^9/l	Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg

When Neutrophils	Recommended Course
< 0,5 x 10^9/l for ≥ 7 days or <	Interrupt Revlimid treatment

$0,5 \times 10^9$/l associated with fever (≥ 38,5 °C)

Return to ≥ $0,5 \times 10^9$/l Resume Revlimid at 5 mg once a day continuously in repeating 28 day cycles + Absolute neutrophil count

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily

When Neutrophils	Recommended Course
< $0,5 \times 10^9$/l for ≥ 7 days or < $0,5 \times 10^9$/l associated with fever (≥ 38,5°C)	Interrupt Revlimid treatment
Return to ≥ $0,5 \times 10^9$/l	Resume Revlimid at 5 mg every other day

+ Absolute neutrophil count

Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to Revlimid, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2 at the medical practitioner's discretion.

Discontinuation of Revlimid

Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash.

Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation from these reactions.

Multiple Myeloma

Previously Treated Multiple Myeloma

Recommended dosage:

The recommended starting dose of Revlimid is 25 mg/day orally on Days 1-21 of repeated 28-day cycles for multiple myeloma. The recommended dose of dexamethasone is 40 mg/day 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/day orally on Days 1-4 every 28 days. Treatment should be continued until disease progression or unacceptable toxicity.

Recommended dose adjustments during treatment and restart of treatment:

Dose modification guidelines, 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.

Platelet counts

Thrombocytopenia

See table below entitled, ‘Dose Reduction Steps for Revlimid in Previously Treated Multiple Myeloma’

Neutrophil counts (ANC)

Neutropenia

See table below entitled, ‘Dose Reduction Steps for Revlimid in Previously Treated Multiple Myeloma’

Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to Revlimid, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2 at the medical practitioner's discretion.

Discontinuation of Revlimid

Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash. Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation from these reactions.

Recommended dose adjustment for previously treated multiple myeloma:

Dosing is continued or modified based upon clinical and laboratory findings.

Dose Reduction Steps for Revlimid in Previously Treated Multiple Myeloma:

Platelet counts

Thrombocytopenia

			Previously Treated Multiple Myeloma (combination with dexamethasone)
			Days 1-21/28 day cycle
When platelets	**Recommended Course**	**Dose Levels**	
Fall to < 30 x 10^9/l	Interrupt Revlimid treatment and follow CBC weekly	Starting Dose	25 mg

Return to ≥ 30 x 10^9/l	Resume Revlimid at dose level -1	Dose Level -1	15 mg
For each subsequent drop below < 30 x 10^9/l Return to ≥ 30 x 10^9/l	Interrupt Revlimid treatment Resume Revlimid at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest Revlimid dose level in the indicated dose regimen.	Dose Level -2	10 mg
		Dose Level -3	5 mg

Absolute neutrophil counts (ANC) Neutropenia

When neutrophils	**Recommended Course[a]**	**Dose Level**	**Previously Treated Multiple Myeloma (combination with dexamethasone)** **Days 1-21/28 day cycle**
Fall to < 0,5 x 10^9/l	Interrupt Revlimid treatment and follow CBC weekly	Starting Dose	25 mg
Return to ≥ 0,5 x 10^9/l	Resume Revlimid at dose level -1	Dose Level -1	15 mg
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 the next lower dose level -2 or -3 for the indicated dose regimen.	Dose Level -2	10 mg
		Dose Level -3	5 mg

	Do not dose below the lowest Revlimid dose level in the indicated dose regimen.		

a At the medical practitioner's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of Revlimid.

Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to Revlimid, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2 at the medical practitioner's discretion.

Discontinuation of Revlimid

Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash. Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions.

Paediatrics:

No data are available supporting the use in paediatric patients below the age of 18.

Elderly:

No dose adjustments needed. Because elderly patients are more likely to have decreased renal function, and Revlimid is cleared by the kidney, care should be taken in dose selection (see 'use in patients with impaired renal function').

Use in Patients with Impaired Renal Function:

Revlimid is primarily excreted unchanged 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 creatinine clearance (CLcr) ≥ 60 ml/min. The following Revlimid dose adjustments are recommended at the start of therapy for patients with CLcr < 60 ml/min.

Renal Function (CLcr)	**Starting dose 25 mg**	**Starting dose 10 mg**
Moderate Renal Impairment (30 > CLcr < 60 ml/min)	10 mg[a] Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg Every 48 hours	5 mg Every 48 hours
End Stage Renal Disease (CLcr < 30 ml/min, requiring dialysis)	5 mg Once daily. On dialysis days the dose should be administered following dialysis	5 mg 3 times a week following each dialysis

CLcr = creatinine clearance [a]The dose may be escalated to 15 mg every 24 hours after 2 cycles if patient is not responding to treatment and is tolerating the medicine.

After initiation of Revlimid therapy, subsequent Revlimid dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

Use in Patients with Impaired Hepatic Function

No study has been conducted in patients with hepatic impairment. Revlimid is not known to be metabolised by the liver; the elimination of unchanged Revlimid is predominantly by the renal route (see 'Pharmacokinetics').

SIDE EFFECTS:

Overall reported Adverse Drug Reactions (ADR's) in Relapsed and Refractory Multiple Myeloma and Myelodysplastic Syndromes:

Adverse reactions observed in patients are listed below by system organ class/preferred term and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000 including isolated reports).

System Organ Class/ Preferred Term	**Frequency of ADRs**	**All ADRs**	**Grade 3/4 ADRs**	**SADRs**
General disorders and administration site conditions				
	Very Common	Pyrexia, oedema (including peripheral), influenza like illness syndrome (including pyrexia, cough, rhinitis, myalgia, musculoskeletal pain, pharyngitis, headache and rigors), fatigue, asthenia,		
	Common	Chest pain	Fatigue, pyrexia, asthenia, fall	
Gastrointestinal Disorders				
	Very Common	Diarrhoea[@], vomiting[@], nausea[@], constipation, abdominal pain (including upper)[@],		
	Common	Dry mouth, dyspepsia	Diarrhoea[@], nausea[@], constipation, toothache	Diarrhoea[@],
Musculoskeletal and connective				

System Organ Class/ Preferred Term	Frequency of ADRs	All ADRs	Grade 3/4 ADRs	SADRs
tissue disorders				
	Very Common	Musculoskeletal and connective tissue pain and discomfort (including back pain and pain in extremity), bone pain, muscle spasms, arthralgia, myalgia		
	Common		Muscular weakness, musculoskeletal and connective tissue pain and discomfort, back pain	Back pain
Nervous System disorders				
	Very Common	Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysguesia, headache		
	Common	Lethargy, paraesthesia	Syncope, dizziness	Cerebrovascular accident[@]
Respiratory, Thoracic and Mediastinal Disorders				
	Very Common	Dyspnoea, epistaxis		
	Common		Respiratory distress[@,] , bronchitis	
Infections and Infestations [#]				
	Very Common	Pneumonia[@,] bronchitis, bacterial, viral and fungal infections (including opportunistic infections), upper respiratory tract infection		Pneumonia[@]

System Organ Class/ Preferred Term	Frequency of ADRs	All ADRs	Grade 3/4 ADRs	SADRs
	Common	Sinusitis	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections)	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections)
Skin and Subcutaneous tissue Disorders				
	Very Common	Rash[+], pruritus, dry skin		
	Common	Hyperhidrosis	Rash, pruritus	
Blood and Lymphatic System Disorders				
	Very Common	Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia	Neutropenia[%], thrombocytopenia[@] anaemia[@], leukopenia	
	Common		Febrile neutropenia[%],	Anaemia[@], febrile neutropenia[%], neutropenia[%], thrombocytopenia[@]
Metabolism and Nutrition Disorders				
	Very Common	Decreased appetite, hypokalaemia		
	Common	Hypocalcaemia, dehydration, dypomagnesaemia, iron overload	Hypokalaemia, hypocalcaemia, hypophosphataemia, hyperglycaemia[%], decreased appetite	Hyperglycaemia[%]

Eye Disorders				
	Very Common	Blurred vision		
	Common		Cataracts	
Renal Disorders				
	Common		Renal failure@	Renal failure@
Vascular Disorders				
System Organ Class/ Preferred Term	**Frequency of ADRs**	**All ADRs**	**Grade 3/4 ADRs**	**SADRs**
	Very Common	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism@	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism@	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism@
	Common	Hypertension, hypotension, haematoma		
Psychiatric Disorder				
	Common		Depression	Altered mood
Cardiac Disorder				
	Common		Acute myocardial infarction@, atrial fibrillation@, tachycardia, cardiac failure congestive@, cardiac failure@	Acute myocardial infarction@, atrial fibrillation@, cardiac failure congestive@, cardiac failure@
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
	Common			B-cell lymphomas
Immune System Disorders				
	Uncommon	Hypersensitivity		

Hepatobiliary Disorders				
	Common	Abnormal liver function tests	Abnormal liver function tests	Abnormal liver function tests
Investigations				
	Common	Decreased weight		

@ - ADRs with Death as an outcome
% - ADRs which were considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
# - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
+-All PTs under HLT of Rash will be considered listed

Post-Marketing Data

The following adverse drug reactions have been identified from the worldwide postmarketing experience with Revlimid. Allergic conditions[1] (angioedema, SJS, TEN), tumour lysis syndrome (TLS) and tumour flare reaction (TFR), pneumonitis, and transient abnormal liver laboratory tests have been reported, but the frequency is unknown.

Hepatic Disorders

Transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with Revlimid. Treatment with Revlimid should be interrupted and restarted once the levels return to baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

[1] All PTs under MedDRA SMQ of Severe Cutaneous ADRs and HLT rash, and All PTs under HLGT Angioedema and Urticaria will be considered listed

There is no specific experience in the management of Revlimid overdose in patients. In studies, the dose-limiting toxicity was essentially haematological. In the event of overdose, supportive care is advised.

IDENTIFICATION:

Revlimid 5 mg hard capsules: White to off-white, opaque size 2 hard gelatin capsule with a black imprint of 'REV' and '5 mg'.

Revlimid 10 mg hard capsules: Pale yellow opaque body, blue green opaque cap, size 0, hard gelatin capsule with a black imprint of 'REV' and '10 mg'.

Revlimid 15 mg hard capsules: White to off-white opaque body, powder blue opaque cap, size 0, hard gelatin capsule with a black imprint of 'REV' and '15 mg'. Revlimid 25 mg hard capsules: White to off-white, opaque size 0 hard gelatin capsule with a black imprint of 'REV' and '25 mg'.

PRESENTATION:

Clear, transparent Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters, each with seven capsules. There will be either 1, 3 or 4 blisters in each pack, dependent on pack size (either 7, 21 or 28 capsules), packed in a cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC. Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

Revlimid 5 mg: 47/32/0507

Revlimid 10 mg: 47/32/0508

Revlimid 15 mg: 47/32/0509 Revlimid

25 mg: 47/32/0510

NAME AND BUSINESS ADDRESS OF THE REGISTRATION HOLDER:

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Johannesburg

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