VILENA

Lenalidomide

Capsules 2.5 mg
Capsules 5 mg
Capsules 7.5 mg
Capsules 10 mg
Capsules 15 mg
Capsules 20 mg
Capsules 25 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vilena 2.5 mg capsules	: Each capsule contains 2.5 mg of lenalidomide.
Vilena 5 mg capsules	: Each capsule contains 5 mg of lenalidomide.
Vilena 7.5 mg capsules	: Each capsule contains 7.5 mg of lenalidomide.
Vilena 10 mg capsules	: Each capsule contains 10 mg of lenalidomide.
Vilena 15 mg capsules	: Each capsule contains 15 mg of lenalidomide.
Vilena 20 mg capsules	: Each capsule contains 20 mg of lenalidomide.
Vilena 25 mg capsules	: Each capsule contains 25 mg of lenalidomide.

PHARMACEUTICAL FORM

Vilena 2.5 mg capsules
Hard gelatin capsule, with an opaque white body and opaque green cap with “L9NL” and “2.5” printed radial on body. Capsule size : 4

Vilena 5 mg capsules
Hard gelatin capsule, with an opaque white body and opaque white cap with “L9NL” and “5” printed radial on body. Capsule size : 2

Vilena 7.5 mg capsules
Hard gelatin capsule, with an opaque white body and opaque yellow cap with “L9NL” and “7.5” printed radial on body. Capsule size : 2

Vilena 10 mg capsules
Hard gelatin capsule, with an opaque yellow body and opaque green cap with “L9NL” and “10” printed radial on body. Capsule size : 0

Vilena 15 mg capsules
Hard gelatin capsule, with an opaque white body and opaque blue cap with “L9NL” and “15” printed radial on body. Capsule size : 0

Vilena 20 mg capsules
Hard gelatin capsule, with an opaque blue body and opaque green cap with “L9NL” and “20” printed radial on body. Capsule size : 0

Vilena 25 mg capsules
Hard gelatin capsule, with an opaque white body and opaque white cap with “L9NL” and “25” printed radial on body. Capsule size : 0

THERAPEUTIC INDICATIONS

Multiple myeloma

DISETUJUI OLEH BPOM : 25/10/2024

ID : EREG10019112400159
EREG10019112400161
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Vilena as combination therapy with dexamethasone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Vilena as combination therapy with melphalan and prednisone is indicated for the treatment of ≥ 65 years old patients with previously untreated multiple myeloma who are not eligible for transplant.

Vilena in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have relapsed or have progressive disease after receiving at least one prior therapy.

Myelodysplastic syndromes
Vilena as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia 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.

Mantle cell lymphoma
Vilena as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

POSOLOGY AND METHOD OF ADMINISTRATION

Vilena treatment should be supervised by a physician experienced in the use of anti-cancer therapies. For all indications described below:

- Dose is modified based upon clinical and laboratory findings
- Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
- In case of neutropenia, the use of growth factors in patient management should be considered.
- 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.

Newly diagnosed multiple myeloma (NDMM)

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose

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, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

- *Dose reduction steps*

	Lenalidomide[a]	Dexamethasone[a]
Starting dose	25 mg	40 mg
Dose level -1	20 mg	20 mg
Dose level -2	15 mg	12 mg
Dose level -3	10 mg	8 mg
Dose level- 4	5 mg	4 mg
Dose level -5	2.5 mg	Not Applicable

[a] Dose reduction for both products can be managed independently

- *Thrombocytopenia*

When platelets	Recommended course
Fall to < 25 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

[a] If Dose Limiting Toxicity (DLT) occurs on > Day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle

- *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide 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 lenalidomide treatment Resume lenalidomide at next lower dose level once daily.

For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥ 1,5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows: 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression.

- *Dose reduction steps*

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose level -2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose level -3	2.5 mg	NA	0.25 mg/kg

[a] If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide

- *Thrombocytopenia*

When platelets	Recommended course
First fall to < 25 x 10^9/L Return to ≥ 25 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide and melphalan at dose level -1
For each subsequent drop below 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily.

- *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L[a] Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide 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 lenalidomide treatment Resume lenalidomide at next lower dose level once daily.

[a]If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of lenalidomide if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle

Multiple myeloma with at least one prior therapy

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Recommended dose

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

Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

- *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 lenalidomide treatment Resume lenalidomide at dose level -1
For each subsequent drop below 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide 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 lenalidomide treatment Resume lenalidomide at starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide 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 lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1,-2 or -3) once daily. Do not dose below 5 mg once daily

Myelodysplastic syndromes (MDS)

Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L and/or platelet counts < 25 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

- *Dose reduction steps*

Starting dose	10 mg once daily on days 1 to 21 every 28 days
Dose level -1	5 mg once daily on days 1 to 28 every 28 days
Dose level -2	2.5 mg once daily on days 1 to 28 every 28 days
Dose level -3	2.5 mg every other day 1 to 28 every 28 days

- *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)

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.

Mantle cell lymphoma (MCL)

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

- *Dose reduction steps*

Starting dose	25 mg once daily on days 1 to 21, every 28 days
Dose Level -1	20 mg once daily on days 1 to 21, every 28 days
Dose Level -2	15 mg once daily on days 1 to 21, every 28 days
Dose Level -3	10 mg once daily on days 1 to 21, every 28 days
Dose Level -4	5 mg once daily on days 1 to 21, every 28 days
Dose Level -5	2.5 mg once daily on days 1 to 21, every 28 days[1] 5 mg every other day on days 1 to 21, every 28 days

[1] - In countries where the 2.5 mg capsule is available.

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 50 x 10^9/L Return to ≥ 60 x 10^9/L	Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days Resume lenalidomide at next lower level (dose level-1)
For each subsequent drop below 50 x 10^9/L Return to ≥ 60 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days Resume lenalidomide at next lower level (dose level -2, -3, -4, -5). Do not dose below dose level-5

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 1 x 10^9/L for at least 7 days or Falls to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥ 1 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt lenalidomide treatment

Tumour flare reaction
Lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

All indications
For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted 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 (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptomps (DRESS) is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population
Vilena should not be used in children and adolescents from birth to less than 18 years because of safety concerns.

Elderly
Currently available pharmacokinetic data are described in Pharmacokinetic properties. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age, in myelodysplastic syndromes patients up to 95 years of age and in mantle cell lymphoma patients up to 88 years of age.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Newly diagnosed multiple myeloma: patients who are not eligible for transplant
Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered. For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg once daily on days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years who are treated with lenalidomide in combination with melphalan and prednisone. In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation.
Lenalidomide combined therapy was less tolerated in newly diagnosed multiple myeloma patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years.

Multiple myeloma : patients with at least one prior therapy
The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

Myelodysplastic syndromes
For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Mantle cell lymphoma
For mantle cell lymphoma patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged 65 years or over compared with patients aged under 65 years of age.

Patients with renal impairment
Lenalidomide is primarily excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance. 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 and multiple myeloma, myelodysplastic syndromes or mantle cell lymphoma.
The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.
There are no phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

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] 15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5 mg 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.

Myelodysplastic syndromes

Renal function (CLcr)	**Dose adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	Starting dose	5 mg once daily (days 1 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg once daily (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg once every other day (days 1 to 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 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1 to 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 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1 to 28 of repeated 28-day cycles)

* Recommended dose reduction steps during treatment and restart of treatment to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide, as described above.

Mantle cell lymphoma

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] 15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5 mg 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.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

Patients with hepatic impairment
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Method of administration
Oral use.
Vilena capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Program are met

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pregnancy warning

Lenalidomide 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.If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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

Criteria for women of non-childbearing potential

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

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

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

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 lenalidomide 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 lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject. As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Vilena or shortly after he has

stopped taking Vilena, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

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

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained 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 bytwo negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended.If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide 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 during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

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 3 days prior to the visit to the prescriber.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment for safe disposal.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, , the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with lenalidomide monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), than in patients with multiple myeloma treated with lenalidomide in combination therapy.

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone. The risk of ATE is lower in patients with multiple myeloma treated with lenalidomide monotherapy than in patients with multiple myeloma treated with lenalidomide in combination therapy.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, 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 lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be 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.

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. In mantle cell lymphoma patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then at the start of each cycle. 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.
Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section Undesirable effects, Haemorrhagic disorders).
Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone*

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm. Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm.

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively).

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone*

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide [MPR+R] and melphalan, prednisone and lenalidomide followed by placebo [MPR+p] treated patients compared with 7.8% in MPp+p-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- *Multiple myeloma: patients with at least one prior therapy*

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone- treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (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).

- *Myelodysplastic syndromes*

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade

3 and 4 neutropenia and thrombocytopenia compared to patients on placebo.

- *Mantle cell lymphoma*

Lenalidomide treatment in mantle cell lymphoma patients is associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

Tumour flare reaction and tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.

Tumour burden
- *Mantle cell lymphoma*

Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available.

Early death
In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, there were 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (40%) and 6/28 (21%).

Adverse events
In study MCL-002, during treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).
Patients with high tumour burden should therefore be closely monitored for adverse reactions including signs of tumour flare reaction (TFR). Please refer to section Posology and Method of Administration for dose adjustments for TFR. High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tumour flare reaction
- *Mantle cell lymphoma*

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient.

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide. 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
Severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptomps. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS 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.

Lactose intolerance
Vilena capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 person-years) compared to controls (1.38 per 100 person-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 patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Vilena in this setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

- *Karyotype*

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of lenalidomide when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- *TP53* status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038).

Progression to other malignancies in mantle cell lymphoma
In mantle cell lymphoma, AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are potential risks.

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT in patients with NDMM who are not eligible for transplant, and with lenalidomide maintenance compared to placebo in patients with NDMM who had undergone ASCT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Viral reactivation
Cases of viral reactivation have been reported in patients receiving lenalidomide, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

Some of the cases of viral reactivation had a fatal outcome.

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster requiring a temporary hold or permanent discontinuation of the treatment with lenalidomide and adequate antiviral treatment.

Reactivation of hepatitis B has been reported rarely in patients receiving lenalidomide who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure resulting in discontinuation of lenalidomide and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.
Caution should be exercised when lenalidomide is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Newly diagnosed multiple myeloma patients

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS equal or more than 2 or CLcr less than 60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS equal or more than 2 or CLcr less than 60 mL/min.

Cataract

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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 lenalidomide with dexamethasone.

Oral contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken.

Warfarin

Co-administration of multiple 10 mg doses of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (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 the treatment.

Digoxin

Concomitant administration with lenalidomide 10 mg once daily increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the clinical use (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

Statins

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of

treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg/ once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ once daily).
Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

FERTILITY, PREGNANCY AND LACTATION

Due to the teratogenic potential, lenalidomide must be prescribed under a Pregnancy Prevention Program, unless there is reliable evidence that the patient does not have childbearing potential.

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject. As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide 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. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.

Breast-feeding
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone
The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low

dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone
The serious adverse reactions observed more frequently (≥5%) with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan, prednisone and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma: patients with at least one prior therapy
In two phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Grade 4 neutropenia.

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes
The overall safety profile of lenalidomide in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one phase II study and one phase III study. In the phase II, all 148 patients were on lenalidomide treatment. In the phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section Special warnings and precautions for use)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section Special warnings and precautions for use).

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Mantle cell lymphoma

The overall safety profile of lenalidomide in patients with mantle cell lymphoma is based on data from 254 patients from a phase II randomised, controlled study MCL-002.
Additionally, adverse drug reactions from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were:

- Neutropenia (3.6%)
- Pulmonary embolism (3.6%)
- Diarrhoea (3.6%)

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in study MCL-002 were neutropenia (50.9%), anemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%).
During treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%). High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with lenalidomide are listed below by system organ class 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), not known (cannot be estimated from the available data).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Tabulated summary for combination therapy in MM
The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the longer duration of treatment in the lenalidomide-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies.

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia◊, Upper respiratory tract infection◊, Bacterial, viral and fungal infections (including opportunistic infections) ◊, Nasopharyngitis, Pharyngitis, Bronchitis◊ Common Sepsis◊, Sinusitis◊	Common Pneumonia◊, Bacterial, viral and fungal infections (including opportunistic infections) ◊, Sepsis◊, Bronchitis◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma^,◊ Squamous skin cancer^,◊,*	Common Acute myeloid leukaemia◊, Myelodysplastic syndrome◊, Squamous cell carcinoma of

		skin^,◊,** Uncommon T-cell type acute leukaemia◊, Basal cell carcinoma^,◊, Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia^,◊, Thrombocytopenia ^,◊, Anemia◊, Haemorrhagic disorder ^, Leucopenias Common Febrile neutropenia^,◊, Pancytopenia◊ Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia	Very Common Neutropenia^,◊, Thrombocytopenia^,◊, Anemia◊, Leucopenias Common Febrile neutropenia^,◊, Pancytopenia◊, Haemolytic Anemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity^	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia◊, Hyperglycaemia, Hypocalcaemia◊, Decreased appetite, Weight Decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration◊, Hypercalaemia+	Common Hypokalaemia◊, Hyperglycaemia, Hypocalcaemia◊, Diabetes mellitus◊, Hypophosphataemia, Hyponatraemia◊, Hyperuricaemia, Gout, Decreased appetite, Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache, Paresthesia Common Ataxia, Balance impaired, Neuralgia, Dysaesthesia	Common Cerebrovascular accident◊, Dizziness, Syncope, Neuralgia Uncommon Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	

Cardiac Disorders	Common Atrial fibrillation◊, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute)^, ◊, Atrial fibrillation◊, Congestive cardiac failure◊, Tachycardia, Cardiac failure◊, Myocardial ischaemia◊
Vascular Disorders	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊ Common Hypotension◊, Hypertension, Ecchymosis^	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊, Epistaxis^, Cough Common Dysphonia	Common Respiratory distress◊, Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea◊, Constipation◊, Abdominal pain◊, Nausea, Vomiting, Dyspepsia, Dry mouth, Stomatitis Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dysphagia Uncommon Colitis, Caecitis	Common Gastrointestinal haemorrhage, Diarrhoea◊, Constipation◊, Abdominal pain◊, Nausea, Vomiting
Hepatobiliary Disorders	Very common Alanine aminotransferase increased, Aspartate aminotransferase increased Common Abnormal liver function tests◊, Hyperbilirubinemia Uncommon Hepatic failure^	Common Cholestasis◊, Abnormal liver function tests◊, Hepatotoxicity, Alanine aminotransferase increased Uncommon Hepatic failure^

Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊), Arthralgia◊, Pain in extremity, Myalgia Common Muscular weakness, Joint swelling	Common Muscular weakness, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊) Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute) ◊ Common Haematuria^, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue◊, Oedema (including peripheral oedema), Pyrexia◊, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy	Very Common Fatigue◊ Common Oedema peripheral, Pyrexia◊, Asthenia
Investigations	Very common Blood alkaline phosphatase increased Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

^See section Undesirable effects, description of selected adverse reactions

◊Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

+ Applies to serious adverse drug reactions only

* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

**Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary from monotherapy
The following tables are derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes and mantle cell lymphoma.

Table 2. ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)◊	Very Common Pneumonia◊ Common Bacterial, viral and fungal infections (including opportunistic infections) ◊ , Bronchitis
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Leucopenias	Very Common Thrombocytopenia^◊, Neutropenia^◊, Leucopenias Common Febrile neutropenia^◊
Endocrine Disorders	Very Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Decreased appetite Common Iron overload, Weight decreased	Common Hyperglycaemia◊, Decreased appetite
Psychiatric Disorders		Common Altered mood◊,~
Nervous System Disorders	Very Common Dizziness, Headache Common Paraesthesia	
Cardiac Disorders		Common Acute myocardial infarction^,◊, Atrial fibrillation◊, Cardiac failure◊
Vascular Disorders	Common Hypertension, Haematoma	Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Epistaxis^	
Gastrointestinal Disorders	Very Common Diarrhoea◊, Abdominal pain (including upper), Nausea, Vomiting, Constipation	Common Diarrhoea◊, Nausea, Toothache

	Common Dry mouth, Dyspepsia	
Hepatobiliary Disorders	Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Dry Skin, Pruritus	Common Rashes, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Musculoskeletal pain (including back pain◊ and pain in extremity), Arthralgia, Myalgia	Common Back pain◊
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)	Common Pyrexia
Injury, Poisoning and Procedural Complications		Common Fall

^see section Undesirable Effects, description of selected adverse reactions

◊Adverse events reported as serious in myelodysplastic syndromes clinical trials

~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes phase III study; it was not reported as a grade 3 or 4 adverse event

Algorithm applied for inclusion in the SmPC: All ADRs captured by the phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the phase II study algorithm was undertaken and, if the frequency of the ADRs in the phase II study was higher than in the phase III study, the event was included in the EU SmPC at the frequency it occurred in the phase II study.

Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

Table 3. ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency

Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Nasopharyngitis, Pneumonia◊ Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Pneumonia◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer^,◊, Basal cell Carcinoma◊
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^, Neutropenia^,◊, Leucopenias◊, Anemia◊ Common Febrile neutropenia^,◊	Very Common Thrombocytopenia^, Neutropenia^◊, Anemia◊ Common Febrile neutropenia^◊, Leucopenias◊
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation◊	Common Dehydration◊, Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System Disorders	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Myocardial infarction (including acute)^ ◊, Cardiac failure
Vascular Disorders	Common Hypotension◊	Common Deep vein thrombosis◊, pulmonary embolism^◊, Hypotension◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea, Nausea◊, Vomiting◊, Constipation Common Abdominal pain◊	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue	Very Common Rashes (including dermatitis allergic), Pruritus	Common Rashes

Disorders	Common Night sweats, Dry skin	
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness◊	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia◊, Peripheral oedema, Influenza like illness syndrome (including pyrexia◊, cough) Common Chills	Common Pyrexia◊, Asthenia◊, Fatigue

^see section Undesirable Effects description of selected adverse reactions

◊Adverse events reported as serious in mantle cell lymphoma clinical trials Algorithm applied for mantle cell lymphoma:

- Mantle cell lymphoma controlled phase II study
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference inproportion between lenalidomide and control arm
  - All treatment-emergent grade 3 or 4 adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% differencein proportion between lenalidomide and control arm
  - All Serious treatment-emergent adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
- Mantle cell lymphoma single arm phase II study
  - All treatment-emergent adverse events with ≥ 5% of subjects
  - All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects
  - All Serious treatment-emergent adverse events reported in 2 or more subjects

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 4: ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Not known Viral infection, including herpes zoster and hepatitis B virus reactivation	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign,		Rare
Malignant and Unspecified (incl cysts and polyps)		Tumour lysis syndrome
Immune System Disorders	Not known Solid organ transplant rejection	
Blood and Lymphatic System Disorders	Not known Acquired haemophilia	
Endocrine Disorders	Common Hyperthyroidism	

Respiratory, Thoracic and Mediastinal Disorders		Not Known Interstitial pneumonitis
Gastrointestinal Disorders		Not Known Pancreatitis, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations) ^
Hepatobiliary Disorders	Not Known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^	Not Known Acute hepatic failure^, Hepatitis toxic^
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ Not Known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms^

^see section Undesirable effects description of selected adverse reactions

Description of selected adverse reactions

Teratogenicity

Lenalidomide 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 sections Fertility, pregnancy and lactation and Preclinical Safety Data). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone*

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 4 neutropenia (8.5% in Rd and Rd18, compared with MPT (15%). Grade 4 febrile neutropenia was observed infrequently (0.6% in Rd and Rd18 compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18) compared with MPT (11%).

- *Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone*

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of grade 4 neutropenia(34.1% in MPR+R/MPR+p) compared with 13MPp+p (7.8%). There was a higher frequency of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients

is associated with a higher frequency of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

- *Multiple myeloma: patients with at least one prior therapy*

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

- *Myelodysplastic syndromes 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% in 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).

- *Mantle cell lymphoma patients*

In mantle cell lymphoma patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the phase II study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm.

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma., and to a lesser extent in patients treated with melphalan and prednisone or as monotherapy in patients with myelodysplastic syndromes and mantle cell lymphoma treated with lenalidomide monotherapy (see section Interaction with other medicinal products and other forms of interaction).
Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section Special warnings and precautions for use).

Second primary malignancies

In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Acute myeloid leukaemia

- *Multiple myeloma*

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following HDM/ASCT (see section Special warnings and precautions for use). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- *Myelodysplastic syndromes*

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section Special warnings and precautions for use). 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 lenalidomide 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%).

Hepatic disorders
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported.

Tumour flare reaction and tumour lysis syndrome
In study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all report were Grade 1 or 2 in severity and all were assessed as treatment- related. The majority of the events occurred in cycle 1. There were no reports of TLS in study MCL-001.

Gastrointestinal disorders
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

OVERDOSE

There is no specific experience in the management of lenalidomide overdose in patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients

were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants. ATC code:L04AX04.

Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide efficacy and safety have been evaluated in three phase III studies in newly diagnosed multiple myeloma, two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

- *Lenalidomide in combination with dexamethasone in patients who are not eligible for stem cell transplantation*

The safety and efficacy of lenalidomide was assessed in a phase III, multicenter, randomised, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomised (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomisation by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function. Patients >75 years received a dexamethasone dose of 20 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 5:

Table 5: Summary of overall efficacy data

	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)
Investigator-assessed PFS - (months)			
Median[a] PFS time, months (95% CI)[b]	26.0 (20.7, 29.7)	21.0 (19.7, 22.4)	21.9 (19.8, 23.9)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.69 (0.59, 0.80); <0.001		
Rd vs Rd18	0.71 (0.61, 0.83); <0.001		
Rd18 vs MPT	0.99 (0.86, 1.14); 0.866		
PFS2[e] - (months)			
Median[a] PFS2 time, months (95% CI)[b]	42.9 (38.1, 47.4)	40.0 (36.2, 44.2)	35.0 (30.4, 37.8)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.74 (0.63, 0.86); <0.001		
Rd vs Rd18	0.92 (0.78, 1.08); 0.316		
Rd18 vs MPT	0.80 (0.69, 0.93); 0.004		
Overall survival (months)			
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.75 (0.62, 0.90); 0.002		
Rd vs Rd18	0.91 (0.75, 1.09); 0.305		
Rd18 vs MPT	0.83 (0.69, 0.99); 0.034		
Follow-up (months)			
Median[f] (min, max): all patients	40.8 (0.0, 65.9)	40.1 (0.4, 65.7)	38.7 (0.0, 64.2)
Myeloma response[g] n (%)			
CR	81 (15.1)	77 (14.2)	51(9.3)
VGPR	152 (28.4)	154 (28.5)	103(18.8)
PR	169 (31.6)	166 (30.7)	187(34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341(62.3)
Duration of response - (months)[h]			
Median[a] (95% CI)[b]	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IMWG
= International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for □ 18 cycles; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

[a] The median is based on the Kaplan-Meier estimate.

[b] The 95% CI about the median.

[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

[e] Exploratory endpoint (PFS2)

[f] The median is the univariate statistic without adjusting for censoring.

[g] Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category, Data cutoff date = 24 May 2013).

[h] data cut 24 May 2013

- *Lenalidomide in combination with melphalan and prednisone followed by maintenance therapy in patients who are not eligible for transplant*

The safety and efficacy of lenalidomide was assessed in a phase III multicenter, randomised double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study

compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance therapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomised in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1to 4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1to 4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1to 21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance therapy starting with lenalidomide 10 mg orally on days 1to 21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomised to MPR+R, 153 patients randomised to MPR+p and 154 patients randomised to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 6:

Table 6: Summary of overall efficacy data

	MPR+R (N = 152)	**MPR+p (N = 153)**	**MPp +p (N = 154)**
Investigator-assessed PFS - (months)			
Median[a] PFS time, months (95% CI)	27.4 (21.3, 35.0)	14.3 (13.2, 15.7)	13.1 (12.0, 14.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.37 (0.27, 0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35, 0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60, 1.01); 0.059		
PFS2 - (months) [¤]			
Median[a] PFS2 time, months (95% CI)	39.7 (29.2, 48.4)	27.8 (23.1, 33.1)	28.8 (24.3, 33.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.70 (0.54, 0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59, 1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71, 1.19); 0.051		
Overall survival (months)			
Median[a] OS time, months (95% CI)	55.9 (49.1, 67.5)	51.9 (43.1, 60.6)	53.9 (47.3, 64.2)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.95 (0.70, 1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65, 1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79, 1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8, 73.8)	46.3 (0.5, 71.9)	50.4 (0.5, 73.3)
Investigator-assessed Myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)

Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable (NE)	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed Duration of response (CR+PR) - (months)			
Median[a] (95% CI)	26.5 (19.4, 35.8)	12.4 (11.2, 13.9)	12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone;
PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.
[a] The median is based on the Kaplan-Meier estimate

[¤]PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

Supportive newly diagnosed multiple myeloma studies
An open-label, randomised, multicenter, phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomised to the lenalidomide/low dose dexamethasone arm, and 223 were randomised to the lenalidomide/standard dose dexamethasone arm. Patients randomised to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomised to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/ low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy
The efficacy and safety of lenalidomide were evaluated in two phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on days 1 to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the len/dex group and 176 in the placebo/dex group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the len/dex group and 175 in the placebo/dex group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that len/dex was statistically significantly superior (p <

0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the len/dex arm were also significantly higher than the placebo/dex arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dex group to receive treatment with the len/dex combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 7 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with len/dex (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dex (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with len/dex versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dex. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for len/dex and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dex. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the len/dex arm remain significantly higher than in the placebo/dex arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with len/dex versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dex. Despite the fact that 170 out of the 351 patients randomised to placebo/dex received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for len/dex relative to placebo/dex (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 7: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex (N=351)**	
Time to event			**Hazard ratio [95% CI], p-value [a]**
Time to progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001
Progression free survival Median [95% CI], weeks	48.1 [36.4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473], p < 0.001
Overall survival Median [95% CI], weeks 1-year Overall survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0.687, 1.009], p = 0.045
Response rate			**Odds ratio [95% CI], p-value b**
Overall response [n, %] Complete response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a phase 2, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately.

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a

minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).
In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 8. Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent- to-treat populationEndpoint

	MDS-004 N = 205			MDS-003 N = 148
	10 mg† N = 69	5 mg†† N = 69	Placebo* N = 67	10 mg N = 148
Transfusion Independence (≥ 182 days) #	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)
Transfusion Independence (≥ 56 days) #	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to Transfusion Independence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR∞	NR	NR	114.4
Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
# Associated with an increase in Hgb of ≥ 1g/dL
∞ Not reached (i.e. the median was not reached)

In 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%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.
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.
Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.
In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.
A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Mantle cell lymphoma
The efficacy and safety of lenalidomide were evaluated in patients with mantle cell lymphoma in a phase 2, multicenter, randomised open-label study versus single agent of investigator's choice in patients who were refractory to their last regimen or had relapsed one to three times (study MCL-002).
Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomised 2:1 to the lenalidomide or the control

arm. The investigator's choice treatment was selected before randomisation and consisted of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.

Lenalidomide was administered orally 25 mg once daily for the first 21 days (D1 to D21) of repeating 28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.
The baseline demographic were comparable between the lenalidomide arm and control arm. Both patient populations presented a median age of 68.5 years with comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number of prior therapies.
The primary efficacy endpoint in study MCL-002 was progression-free survival (PFS).
The efficacy results for the Intent-to-Treat (ITT) population were assessed by the Independent Review Committee (IRC), and are presented in the table below.

Table 9. Summary of efficacy results – study MCL-002, intent-to-treat population

	Lenalidomide Arm N = 170	**Control Arm** N = 84
PFS		
PFS, median[a] [95% CI][b] (weeks)	37.6 [24.0, 52.6]	22.7 [15.9, 30.1]
Sequential HR [95% CI][e]	0.61 [0.44, 0.84]	
Sequential log-rank test, p-value[e]	0.004	
Response[a], n (%)		
Complete response (CR)	8 (4.7)	0 (0.0)
Partial response (PR)	60 (35.3)	9 (10.7)
Stable disease (SD)[b]	50 (29.4)	44 (52.4)
Progressive disease (PD)	34 (20.0)	26 (31.0)
Not done/Missing	18 (10.6)	5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][c]	68 (40.0) [32.58, 47.78]	9 (10.7)[d] [5.02, 19.37]
p-value[e]	< 0.001	
CRR (CR, CRu), n (%) [95% CI][c]	8 (4.7) [2.05, 9.06]	0 (0.0) [95.70, 100.00]
p-value[e]	0.043	
Duration of Response, median[a] [95% CI] (weeks)	69.6 [41.1, 86.7]	45.1 [36.3, 80.9]
Overall		
Survival HR	0.89 [0.62, 1.28]	
[95% CI][c]		
Log-rank test, p-value	0.520	

CI = confidence interval; CRR = complete response rate; CR = complete response; CRu = complete response unconfirmed; DMC = Data Monitoring Committee; ITT = intent-to-treat; HR = hazard ratio; KM = Kaplan-Meier; MIPI = Mantle Cell Lymphoma International Prognostic Index; NA = not applicable; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR= partial response; SCT = stem cell transplantation; SD = stable disease; SE = standard error.

[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] The mean and median are the univariate statistics without adjusting for censoring.

[d] The stratification variables included time from diagnosis to first dose (< 3 years and ≥ 3 years), time from last prior systemic anti-lymphoma therapy to first dose (< 6 months and ≥ 6 months), prior SCT (yes or no), and MIPI at baseline (low, intermediate, and high risk).

[e] Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based on the difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CI are presented.

In study MCL-002 in the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. In patients with high tumour burden,

corresponding figures were 16/81 (20%) and 2/28 (7%) (see section Special warnings and precautions for use).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Vilena in all subsets of the paediatric population in multiple myeloma.

PHARMACOKINETIC PROPERTIES

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

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 Cmax in plasma. However, in the main multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance.

Biotransformation and elimination
Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro studies indicate that lenalidomide has no inhibitory effect on human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-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.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

Elderly
No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment
The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total lenalidomide clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The Cmax was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section Posology and method of administration

Hepatic impairment
Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

PRECLINICAL SAFETY DATA

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate 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 the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either

the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

Capsule contents
Lactose
Cellulose, microcrystalline (E 460 (i))
Croscarmellose sodium (E 468)
Magnesium stearate (E 470b)

Capsule shell
Gelatin
Titanium dioxide (E171)
Only 2.5 mg, 10 mg, 15 mg, 20 mg: Indigotine (E132)
Only 2.5 mg, 7.5 mg, 10 mg, 20 mg: Yellow iron oxide (E172)

Printing ink
Shellac (E904)
Propylene glycol (E1520)
Black iron oxide (E172)
Potassium hydroxide (E525)

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

2 years

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C

SPECIAL PRECAUTIONS FOR DISPOSAL

Capsules should not be opened or crushed. If powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

PRESENTATION

Vilena 2.5 mg	: Dus, 3 blister @ 7 kapsul	Reg. No. : DKI2043400701A1
Vilena 5 mg	: Dus, 3 blister @ 7 kapsul	Reg. No. : DKI2043400701B1
Vilena 7,5 mg	: Dus, 3 blister @ 7 kapsul	Reg. No. : DKI2043400701C1
Vilena 10 mg	: Dus, 7 blister @ 3 kapsul	Reg. No. : DKI2043400701D1
Vilena 15 mg	: Dus, 7 blister @ 3 kapsul	Reg. No. : DKI2043400701E1
Vilena 20 mg	: Dus, 7 blister @ 3 kapsul	Reg. No. : DKI2043400701F1
Vilena 25 mg	: Dus, 7 blister @ 3 kapsul	Reg. No. : DKI2043400701G1

HARUS DENGAN RESEP DOKTER

Manufactured by:
Synthon Chile Ltda., Santiago – Chile

Released by:
Synthon Hispania S.L., Sant Boi de Llobregat - Spain

Imported by:
PT Pratapa Nirmala, Tangerang - Indonesia

DISETUJUI OLEH BPOM : 25/10/2024

ID : EREG10019112400159
EREG10019112400161
EREG10019112400165

Informasi Produk Untuk Pasien

VILENA 2,5 mg kapsul
VILENA 5 mg kapsul
VILENA 7,5 mg kapsul
VILENA 10 mg kapsul
VILENA 15 mg kapsul
VILENA 20 mg kapsul
VILENA 25 mg kapsul

Lenalidomide

Baca seluruh leaflet ini dengan seksama sebelum mulai penggunaan obat ini.

- Simpanlah leaflet ini, agar dapat dibaca kembali jika diperlukan.
- Jika ada pertanyaan lebih lanjut, hubungi dokter atau apoteker.
- Obat ini diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dikarenakan obat ini dapat saja membahayakan orang lain, walaupun gejala yang dialami sama dengan Anda.
- Jika salah satu efek samping dirasakan menjadi serius atau jika terjadi efek samping apapun yang tidak tercantum di leaflet ini, mohon sampaikan kepada dokter atau apoteker.

Pada leaflet ini terdapat informasi berikut:

1. Apakah VILENA dan kegunaannya

VILENA mengandung zat aktif ‘lenalidomide’. Obat ini termasuk dalam kategori obat yang mempengaruhi kerja sistem imun.

VILENA diberikan untuk orang dewasa untuk:
1. Multiple myeloma
2. Myelodysplastic syndromes (MDS)
3. Mantle cell lymphoma (MCL)

Multiple myeloma
Multiple myeloma adalah jenis kanker yang mempengaruhi jenis sel darah putih tertentu, yang disebut sel plasma. Sel-sel ini berkumpul di sumsum tulang dan membelah, menjadi tidak terkendali. Ini bisa merusak tulang dan ginjal.

Multiple myeloma umumnya tidak dapat disembuhkan. Namun, tanda dan gejalanya dapat sangat berkurang atau hilang untuk jangka waktu tertentu. Ini disebut 'tanggapan'.

<u>Multiple myeloma yang baru didiagnosis - pada pasien yang tidak dapat menjalani transplantasi sumsum tulang.</u>
Vilena diminum dengan obat lain:
- obat anti-inflamasi yang disebut 'deksametason'
- obat kemoterapi yang disebut 'melphalan' dan

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- obat imunosupresan yang disebut 'prednison'.

Pasien akan meminum obat-obatan lain ini pada awal pengobatan dan kemudian melanjutkan untuk meminum Vilena sendiri.

Jika pasien berusia 75 tahun atau lebih atau memiliki masalah ginjal sedang hingga berat - dokter akan memeriksa pasien dengan seksama sebelum memulai pengobatan.

Multiple myeloma - pada pasien yang telah menjalani pengobatan sebelumnya
Vilena diminum bersama dengan obat anti-inflamasi yang disebut 'deksametason'.

Vilena dapat menghentikan tanda dan gejala multiple myeloma yang semakin buruk. Juga terbukti menunda multiple myeloma untuk kambuh kembali setelah pengobatan.

Myelodysplastic syndromes
MDS adalah kumpulan berbagai penyakit sumsum tulang dan darah. Sel-sel darah menjadi tidak normal dan tidak berfungsi dengan baik. Pasien dapat mengalami berbagai tanda dan gejala termasuk jumlah sel darah merah yang rendah (anemia), kebutuhan untuk transfusi darah, dan berresiko infeksi.

Vilena digunakan sendiri untuk mengobati pasien dewasa yang telah didiagnosis dengan MDS, ketika semua hal berikut berlaku:
- Pasien memerlukan transfusi darah rutin untuk mengobati kadar sel darah merah yang rendah (anemia bergantung transfusi)
- Pasien memiliki kelainan sel di sumsum tulang yang disebut 'kelainan sitogenetika penghapusan 5q yang terisolasi'. Ini berarti tubuh pasien tidak membuat cukup sel darah sehat.
- pengobatan lain telah digunakan sebelumnya, tidak cocok atau tidak berfungsi dengan baik.

Vilena dapat meningkatkan jumlah sel darah merah sehat yang diproduksi tubuh dengan mengurangi jumlah sel abnormal:
- ini dapat mengurangi jumlah transfusi darah yang dibutuhkan. Mungkin saja tidak diperlukan transfusi.

Mantle cell lymphoma
MCL adalah kanker bagian dari sistem kekebalan tubuh (jaringan getah bening). Ini mempengaruhi sejenis sel darah putih yang disebut 'B-limfosit' atau sel B. MCL adalah penyakit di mana sel-B tumbuh dalam cara yang tidak terkendali dan menumpuk di jaringan getah bening, sumsum tulang atau darah.

Vilena digunakan sendiri untuk mengobati pasien dewasa yang sebelumnya telah dirawat dengan obat lain.

Bagaimana Vilena bekerja
Vilena bekerja dengan memengaruhi sistem kekebalan tubuh dan secara langsung menyerang kanker. Ini bekerja dalam beberapa cara berbeda:
- dengan menghentikan perkembangan sel kanker
- dengan menghentikan pembuluh darah yang tumbuh di kanker
- dengan merangsang bagian dari sistem kekebalan tubuh untuk menyerang sel-sel kanker.

2. Hal yang harus diperhatikan sebelum pemberian VILENA

VILENA tidak boleh diberikan pada keadaan berikut:

- jika pasien hamil atau berrencana hamil, karena Vilena diperkirakan akan membahayakan anak yang belum lahir (lihat bagian 2, 'Kehamilan, menyusui dan kontrasepsi - informasi untuk wanita dan pria').
- jika pasien kemungkinan bisa hamil, kecuali jika mengikuti semua langkah yang diperlukan untuk mencegah kehamilan (lihat bagian 2, 'Kehamilan, menyusui dan kontrasepsi - informasi untuk wanita dan pria'). Jika pasien kemungkinan bisa hamil, dokter akan mencatat bahwa tindakan yang diperlukan telah diambil dan konfirmasi telah diberikan ke pasien untuk setiap resep yang diberikan.
- jika pasien alergi terhadap lenalidomide atau bahan lain dari obat ini yang tercantum di bagian 6. Jika pasien merasa alergi, mintalah saran dokter.

Jika salah satu dari hal tersebut diatas berlaku untuk pasien, jangan gunakan Vilena. Bicaralah dengan dokter jika tidak yakin.

Berikan perhatian/penanganan khusus untuk VILENA
Bicarakan dengan dokter, apoteker atau perawat sebelum meminum Vilena jika:

- Pasien sebelumnya pernah mengalami bekuan darah - pasien memiliki risiko yang meningkat untuk mengalami pembekuan darah di pembuluh darah dan arteri selama pengobatan.
- Pasien memiliki tanda-tanda infeksi, seperti batuk atau demam
- Pasien terinfeksi virus atau pernah terinfeksi virus sebelumnya, terutama infeksi hepatitis B, varicella zona, HIV. Jika ragu, bicarakan dengan dokter. Pengobatan dengan Vilena dapat menyebabkan virus menjadi aktif kembali, pada pasien yang membawa virus, yang mengakibatkan kambuhnya infeksi. Dokter harus memeriksa apakah pasien pernah memiliki infeksi hepatitis B.
- Pasien memiliki masalah ginjal - dokter akan menyesuaikan dosis Vilena
- Pasien pernah mengalami serangan jantung, pernah mengalami pembekuan darah, atau jika pasien merokok, memiliki tekanan darah tinggi atau kadar kolesterol tinggi
- Pasien memiliki reaksi alergi saat menggunakan thalidomide (obat lain yang digunakan untuk mengobati multiple myeloma) seperti ruam, gatal, bengkak, pusing, atau sulit bernapas
- Pasien pernah mengalami kombinasi gejala-gejala berikut: ruam di wajah atau ruam yang memanjang, kulit merah, demam tinggi, gejala mirip flu, pembesaran kelenjar getah bening (tanda-tanda reaksi kulit yang parah yang disebut reaksi obat dengan eosinofilia dan gejala sistemik (DRESS), lihat juga bagian 4 "Kemungkinan efek samping").

Jika salah satu di atas dialami pasien, beri tahu dokter sebelum memulai pengobatan.

Jika pasien mengalami MDS, pasien lebih memungkinkan untuk mengalami kondisi lebih lanjut yang disebut leukemia myeloid akut (AML). Selain itu, tidak diketahui bagaimana Vilena mempengaruhi kondisi pasien untuk mengalami AML. Karena itu dokter dapat melakukan tes untuk memeriksa tanda-tanda yang memprediksi kemungkinan pasien mengalami AML selama pengobatan dengan Vilena.

Kapan saja selama atau setelah pengobatan, beri tahu dokter atau perawat segera jika pasien: mengalami penglihatan kabur, kehilangan penglihatan atau penglihatan ganda, kesulitan berbicara, kelemahan pada lengan atau kaki, perubahan cara pasien berjalan atau masalah dengan keseimbangan pasien, mati rasa terus-menerus, penurunan rasa atau kehilangan rasa, kehilangan memori atau kebingungan. Ini semua mungkin merupakan gejala kondisi otak yang serius dan

berpotensi fatal yang dikenal sebagai progresif multifocal leukukoensefalopati (PML). Jika pasien memiliki gejala-gejala ini sebelum pengobatan dengan lenalidomide, beri tahu dokter tentang perubahan dalam gejala-gejala ini.

Tes dan pemeriksaan
Sebelum dan selama pengobatan dengan Vilena, pasien akan menjalani tes darah secara teratur karena Vilena dapat menyebabkan penurunan sel darah yang membantu melawan infeksi (sel darah putih) dan membantu darah membeku (trombosit).

Dokter akan meminta pasien untuk melakukan tes darah:
- sebelum pengobatan
- setiap minggu selama 8 minggu pertama pengobatan
- lalu setidaknya setiap bulan setelah itu.

<u>Untuk pasien dengan MCL yang meminum Vilena</u>
Dokter akan meminta pasien untuk melakukan tes darah:
- sebelum pengobatan
- setiap minggu selama 8 minggu pertama (2 siklus) pengobatan
- lalu setiap 2 minggu dalam Siklus 3 dan 4 (lihat Bagian 3 'Siklus Pengobatan' untuk informasi lebih lanjut)
- setelahnya pada awal setiap siklus dan
- setidaknya setiap bulan

Dokter akan memeriksa apakah pasien memiliki jumlah total tumor yang tinggi di seluruh tubuh, termasuk dalam sumsum tulang. Ini dapat menyebabkan kondisi di mana tumor rusak dan menyebabkan tingkat bahan kimia yang tidak biasa dalam darah yang dapat menyebabkan gagal ginjal (kondisi ini disebut 'Tumor Lysis Syndrome').

Dokter mungkin akan memeriksa pasien untuk perubahan pada kulit pasien seperti bintik-bintik merah atau ruam.

Dokter dapat menyesuaikan dosis Vilena atau menghentikan pengobatan berdasarkan hasil tes darah pasien dan kondisi umum pasien. Jika pasien baru didiagnosis, dokter juga dapat menentukan pengobatan berdasarkan usia pasien dan kondisi lain dari pasien.

Donor darah
Pasien tidak boleh mendonorkan darah selama pengobatan dan selama 1 minggu setelah pengobatan berakhir.

Anak-anak dan remaja
Vilena tidak direkomendasikan untuk digunakan pada anak-anak dan remaja di bawah 18 tahun.

Lansia dan pasien dengan gangguan ginjal
Jika pasien berusia 75 tahun atau lebih atau memiliki gangguan ginjal sedang hingga berat - dokter akan memeriksa pasien dengan seksama sebelum memulai pengobatan.

Obat-obatan lain dan Vilena
Beri tahu dokter atau perawat jika pasien sedang minum obat-obatan lain. Ini karena Vilena dapat mempengaruhi cara kerja beberapa obat lain. Juga, beberapa obat lain dapat mempengaruhi cara kerja Vilena.

Secara khusus, beri tahu dokter atau perawat jika pasien sedang mengonsumsi obat-obatan berikut:
- obat-obatan yang digunakan untuk mencegah kehamilan seperti kontrasepsi oral

- obat-obatan yang digunakan untuk masalah jantung - seperti digoxin
- obat-obatan yang digunakan untuk mengencerkan darah - seperti warfarin

Kehamilan, menyusui dan kontrasepsi - informasi untuk wanita dan pria

Untuk wanita yang meminum Vilena

- Pasien wanita tidak boleh meminum Vilena jika sedang hamil, karena dapat membahayakan bayi yang belum lahir.
- Pasien wanita tidak boleh hamil saat meminum Vilena. Karena itu pasien harus menggunakan metode kontrasepsi yang efektif jika pasien seorang wanita yang berpotensi memiliki anak (lihat 'Kontrasepsi' di bawah).
- Jika pasien wanita menjadi hamil selama pengobatan dengan Vilena, wanita tersebut harus menghentikan pengobatan dan segera memberi tahu dokter.

Untuk pria yang meminum Vilena

- Jika pasangan dari pasien pria tersebut hamil saat pasien mengonsumsi Vilena, pasien pria tersebut harus segera memberi tahu dokter. Disarankan pasangan pria tersebut juga berkonsultasi ke dokter.
- Pasien pria juga harus menggunakan metode kontrasepsi yang efektif (lihat 'Kontrasepsi' di bawah).

Menyusui

Pasien wanita tidak boleh menyusui saat meminum Vilena, karena tidak diketahui apakah Vilena juga terkandung dalam ASI.

Kontrasepsi

Untuk wanita yang meminum Vilena

Sebelum memulai pengobatan, tanyakan kepada dokter apakah pasien wanita bisa hamil, bahkan jika sepertinya tidak mungkin akan hamil.

Jika pasien wanita bisa hamil:

- Pasien wanita tersebut akan menjalani tes kehamilan di bawah pengawasan dokter (sebelum setiap pengobatan, setiap 4 minggu selama pengobatan, dan 4 minggu setelah pengobatan selesai) kecuali dalam kondisi tuba falopi telah dipotong dan diikat, untuk menghentikan sel telur mencapai rahim (sterilisasi tuba)

DAN

- Pasien wanita harus menggunakan metode kontrasepsi yang efektif selama 4 minggu sebelum memulai pengobatan, selama pengobatan, dan sampai 4 minggu setelah menghentikan pengobatan. Dokter akan memberi tahu pasien tentang metode kontrasepsi yang tepat.

Untuk pria yang meminum Vilena

Vilena terkandung dalam air mani manusia. Jika pasangan wanita dari pasien pria hamil atau bisa hamil, dan dia tidak menggunakan metode kontrasepsi yang efektif, pasien pria tersebut harus menggunakan kondom selama pengobarab dan 1 minggu setelah pengobatan berakhir, bahkan jika pasien pria tersebut telah menjalani vasektomi.

Mengemudi dan menggunakan mesin

Jangan mengemudi atau mengoperasikan mesin jika pasien merasa pusing, lelah, mengantuk, memiliki vertigo atau penglihatan kabur setelah meminum Vilena.

Vilena mengandung laktosa

Jika pasien telah diberitahu oleh dokter bahwa pasien tersebut memiliki intoleransi terhadap beberapa gula, hubungi dokter sebelum minum obat ini.

3. Bagaimana cara VILENA diberikan

Vilena harus diberikan kepada pasien oleh profesional kesehatan dengan pengalaman dalam mengobati multiple myeloma, MDS atau MCL.

Selalu minum Vilena persis seperti yang dikatakan dokter. Jika pasien menggunakan Vilena dalam kombinasi dengan obat-obatan lain, pasien harus merujuk pada leaflet obat-obatan ini untuk informasi lebih lanjut tentang penggunaan dan efeknya.

Siklus pengobatan
Vilena diminum pada hari-hari tertentu selama 4 minggu (28 hari).

- Setiap 28 hari disebut 'siklus pengobatan'.
- Bergantung pada hari siklus, pasien akan minum satu atau lebih obat-obatan. Namun, pada beberapa hari pasien tidak minum obat apa pun.
- Setelah menyelesaikan setiap siklus 28 hari, pasien harus memulai 'siklus' baru selama 28 hari berikutnya.

Berapa banyak Vilena yang harus diminum
Sebelum pasien memulai pengobatan, dokter akan memberi tahu pasien:

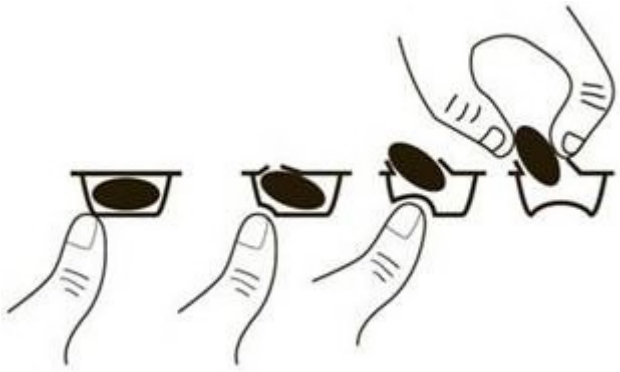
- berapa banyak Vilena yang harus diminum
- berapa banyak obat lain yang harus digunakan dalam kombinasi dengan Vilena, jika ada
- pada hari apa siklus pengobatan dimulai.

Bagaimana dan kapan harus meminum Vilena

- telan kapsul utuh dengan bantuan air.
- jangan merusak, membuka atau mengunyah kapsul. Jika bubuk dari kapsul Vilena yang rusak kontak dengan kulit, segera cuci kulit dengan sabun dan air.
- kapsul dapat dikonsumsi dengan atau tanpa makanan.
- pasien harus meminum Vilena pada waktu yang sama pada hari-hari yang dijadwalkan.

Cara minum Vilena
Untuk mengeluarkan kapsul dari blister:

- tekan hanya satu ujung kapsul untuk mendorongnya melewati foil
- jangan menekan bagian tengah kapsul, karena dapat menyebabkannya pecah.



Lama pengobatan dengan Vilena
Vilena diminum dalam siklus pengobatan, setiap siklus berlangsung selama 28 hari (lihat di atas 'Siklus pengobatan'). Pasien harus melanjutkan siklus pengobatan sampai dokter memberi tahu untuk berhenti.

Jika pasien meminum lebih banyak Vilena dari yang seharusnya
Jika pasien meminum lebih banyak Vilena daripada yang diresepkan, segera beri tahu dokter.

Jika pasien lupa untuk meminum Vilena
Jika pasien lupa untuk meminum Vilena pada waktu biasa pasien minum dan jika

- kurang dari 12 jam - segera minum Vilena.
- lebih dari 12 jam - jangan minum Vilena. Minumlah kapsul Vilena berikutnya pada waktu yang biasa di hari berikutnya.

Jika pasien memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker.

4. Kemungkinan efek samping yang terjadi

Seperti halnya obat-obatan lainnya, VILENA dapat menyebabkan efek samping, walaupun tidak semua orang akan mengalaminya.

Efek samping serius yang dapat dialami lebih dari 1 dari 10 orang (sangat umum)
Vilena dapat mengurangi jumlah sel darah putih yang melawan infeksi dan juga sel darah yang membantu pembekuan darah (trombosit) yang dapat menyebabkan gangguan perdarahan seperti mimisan dan memar.
Vilena juga dapat menyebabkan pembekuan darah di pembuluh darah (trombosis).

Oleh karena itu, pasien harus segera memberi tahu dokter jika mengalami:

- Demam, kedinginan, sakit tenggorokan, batuk, sariawan atau gejala infeksi lainnya termasuk di dalam aliran darah (sepsis)
- Pendarahan atau memar dalam kondisi tidak ada cedera
- Nyeri dada atau sakit kaki
- Sesak napas
- Nyeri tulang
- Kelemahan otot
- Kebingungan atau kelelahan yang mungkin disebabkan oleh tingginya kadar kalsium dalam darah

Efek samping lainnya
Penting untuk dicatat bahwa sejumlah kecil pasien dapat mengembangkan jenis kanker tambahan, dan ada kemungkinan bahwa risiko ini dapat meningkat dengan pengobatan Vilena, oleh karena itu dokter harus hati-hati dalam mengevaluasi manfaat dan risiko ketika pasien diresepkan Vilena.

Efek samping yang sangat umum (dapat dialami lebih dari 1 dari 10 orang):

- Penurunan jumlah sel darah merah yang dapat menyebabkan anemia yang menyebabkan kelelahan dan kelemahan
- Kemerahan pada kulit, ruam
- Kram otot, nyeri otot, nyeri tulang, nyeri sendi
- Pembengkakan menyeluruh termasuk pembengkakan lengan dan kaki
- Lemah dan kelelahan
- Gejala demam dan seperti flu termasuk demam, sakit otot, sakit kepala, sakit telinga, batuk dan kedinginan
- Mati rasa, kesemutan atau sensasi terbakar pada kulit, nyeri di tangan atau kaki, pusing, tremor, nafsu makan menurun, perubahan cara rasa
- Peningkatan rasa nyeri, ukuran tumor atau kemerahan disekitar tumor
- Berat badan menurun
- Sembelit, diare, mual, muntah, nyeri perut, dada seperti terbakar
- Kadar kalium atau kalsium dan atau natrium rendah di darah
- Fungsi tiroid berkurang

- Nyeri tungkai (yang bisa merupakan gejala trombosis), nyeri dada atau sesak napas (yang mungkin merupakan gejala bekuan darah di paru-paru, yang disebut emboli paru)
- Infeksi semua jenis, infeksi paru-paru dan saluran pernapasan bagian atas
- Sesak napas
- Penglihatan kabur
- Mata berkabut (katarak)
- Gangguan ginjal
- Hasil tes fungsi hati tidak normal
- Perubahan pada protein dalam darah yang dapat menyebabkan pembengkakan arteri (vasculitis)
- Peningkatan kadar gula darah (diabetes)
- Sakit kepala
- Hidung berdarah
- Kulit kering
- Depresi, mood berubah, sulit tidur
- Batuk
- Tekanan darah turun
- Tidak enak badan
- Radang tenggorokan, mulut kering
- Dehidrasi
- Sakit perut

Efek samping yang umum (dapat dialami lebih dari 1 dari 10 orang):

- Destruksi sel darah merah (anemia hemolitik)
- Jenis tumor kulit tertentu
- Infeksi sinus yang mengelilingi hidung
- Pendarahan dari gusi, perut, atau usus
- Peningkatan rasa sakit, ukuran tumor, kemerahan di sekitar tumor
- Peningkatan tekanan darah atau penurunan tekanan darah, detak jantung yang lambat, cepat atau tidak teratur
- Peningkatan jumlah senyawa hasil pemecahan sel darah merah bentuk normal dan abnormal
- Peningkatan tipe protein tertentu yang menandakan terjadinya peradangan
- Kulit menjadi lebih gelap
- Peningkatan asam urat dalam darah
- Erupsi kulit, kulit pecah-pecah, kulit mengelupas
- Peningkatan berkeringat
- Sakit radang mulut, mulut kering, susah menelan
- Mulas
- Adanya darah dalam urin
- Produksi urin lebih banyak atau lebih sedikit daripada biasanya (yang mungkin merupakan gejala gagal ginjal), mengeluarkan darah dalam urin
- Napas pendek terutama ketika berbaring (yang mungkin merupakan gejala gagal jantung)
- Kesulitan mendapatkan ereksi
- Stroke, pingsan
- Nyeri dada menyebar ke lengan, leher, rahang, punggung atau perut, terasa berkeringat dan sesak nafas, merasa sakit atau muntah, yang mungkin merupakan gejala serangan jantung (infark miokard)
- Nyeri dada, nyeri leher
- Kelemahan otot
- Pembengkakan sendi
- Aliran empedu dari hati melambat atau tertutup
- Rendahnya kadar fosfat, atau magnesium dalam darah
- Ketulian
- Gangguan keseimbangan, kesulitan bergerak

- Dering di telinga (tinitus)
- Nyeri pada saraf
- Kelebihan zat besi dalam tubuh
- Haus
- Kebingungan
- Sakit gigi
- Jatuh

Efek samping yang tidak biasa (dapat dialami lebih dari 1 dari 100 orang):

- Pendarahan di dalam tengkorak
- Masalah sirkulasi
- Kehilangan penglihatan
- Kehilangan gairah seks (libido)
- Mengalir urin dalam jumlah besar disertai nyeri dan kelemahan tulang, yang mungkin merupakan gejala gangguan ginjal (sindrom Fanconi)
- Pigmentasi kuning pada kulit, selaput lendir atau mata (jaundice), tinja berwarna pucat, urin berwarna gelap, gatal-gatal pada kulit, ruam, nyeri atau bengkak di perut – ini mungkin merupakan gejala cedera pada hati (kelainan hati)
- Nyeri perut, kembung, atau diare, yang mungkin merupakan gejala peradangan di usus besar (disebut kolitis atau caecitis)
- Mengalir urin lebih banyak atau lebih sedikit dari biasanya, yang mungkin merupakan gejala dari gangguan ginjal (disebut nekrosis tubular ginjal)
- Perubahan warna kulit, sensitivitas terhadap sinar matahari
- Ruam, gatal-gatal, bengkak mata mulut atau wajah, sulit bernapas, atau gatal-gatal, yang mungkin merupakan gejala dari reaksi alergi
- Sindrom lisis tumor – komplikasi metabolik yang dapat terjadi selama pengobatan kanker dan kadang-kadang bahkan tanpa pengobatan. Komplikasi ini disebabkan oleh kerusakan produk sel kanker yang sekarat dan mungkin termasuk yang berikut : perubahan kimia darah, tinggi kalium, fosfor, asam urat, dan rendah kalsium menyebabkan perubahan fungsi ginjal, detak jantung, kejang, dan terkadang kematian.
- Ruam yang menyebar, suhu tubuh tinggi, peningkatan enzim hati, kelainan darah (eosinofilia), pembesaran kelenjar getah bening dan keterlibatan organ tubuh lainnya (Reaksi obat dengan eosinofilia dan gejala sistemik yang juga dikenal sebagai DRESS atau sindrom hipersensitivitas obat). Hentikan penggunaan lenalidomide jika pasien mengalami gejala-gejala ini dan hubungi dokter atau segera dapatkan bantuan medis.

Efek samping yang jarang (dapat dialami lebih dari 1 dari 1.000 orang):

- Reaksi alergi serius yang mungkin berawal dari ruam di satu area tetapi menyebar dengan hilangnya kulit secara luas di seluruh tubuh (sindrom Stevens-Johnson dan / atau nekrolisis epidermal toksik).

Tidak dikenal (frekuensi tidak dapat diperkirakan dari data yang tersedia):

- Nyeri mendadak, atau ringan tetapi memburuk di perut bagian atas dan / atau punggung, yang menetap selama beberapa hari, kemungkinan disertai mual, muntah, demam, dan denyut nadi yang cepat. Gejala-gejala ini mungkin karena peradangan pankreas.
- Mengi, sesak napas, atau batuk kering, yang mungkin merupakan gejala yang disebabkan oleh peradangan jaringan di paru-paru.
- Kasus yang jarang terjadi kerusakan otot (nyeri otot, kelemahan atau pembengkakan) yang dapat menyebabkan gangguan ginjal (rhabdomyolysis) telah diamati, beberapa di antaranya ketika Vilena diberikan bersama statin (sejenis obat penurun kolesterol).
- Suatu kondisi yang mempengaruhi kulit yang disebabkan oleh peradangan pembuluh darah kecil, bersama dengan nyeri pada persendian dan demam (leukositoklastik vaskulitis).

- Kerusakan dinding lambung atau usus. Ini dapat menyebabkan infeksi yang sangat serius. Beri tahu dokter jika pasien mengalami sakit perut yang parah, demam, mual, muntah, darah di tinja, atau perubahan kebiasaan buang air besar.
- Infeksi virus, termasuk herpes zoster (juga dikenal sebagai 'sinanaga', penyakit virus yang menyebabkan ruam kulit yang menyakitkan dengan lepuh) dan kambuhnya infeksi hepatitis B (yang dapat menyebabkan kulit dan mata menguning, urin berwarna coklat tua, sakit perut sisi kanan, demam dan merasa mual atau sakit).
- **Penolakan transplantasi organ padat (seperti ginjal, jantung).**

Pelaporan efek samping
Jika pasien mendapat efek samping, bicarakan dengan dokter, apoteker, atau perawat. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, pasien dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan VILENA

- Jauhkan dari jangkauan dan pandangan anak-anak.
- Jangan digunakan setelah tanggal kedaluwarsa yang tercantum pada kemasannya.
- Jangan gunakan obat ini jika terlihat ada kerusakan atau tanda-tanda kerusakan pada kemasan.
- Simpan pada suhu dibawah 30^0C

6. Informasi lainnya

Apa kandungan VILENA
Vilena 2,5 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 2,5 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin, titanium dioksida (E171), indigo carmine (E132) dan yellow iron oxide (E172)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 5 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 5 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin dan titanium dioksida (E171)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 7,5 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 7,5 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin, titanium dioksida (E171) dan yellow iron oxide (E172)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 10 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 10 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat

- cangkang kapsul: gelatin, titanium dioksida (E171), indigo carmine (E132) dan yellow iron oxide (E172)
- tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 15 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 15 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin, titanium dioksida (E171) dan indigo carmine (E132)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 20 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 20 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin, titanium dioksida (E171), indigo carmine (E132) dan yellow iron oxide (E172)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Vilena 25 mg kapsul:
- Zat aktifnya adalah lenalidomide. Setiap kapsul mengandung 25 mg lenalidomide.
- Bahan lainnya adalah:
  - isi kapsul: laktosa anhidrat (lihat bagian 2), selulosa mikrokristalin, croscarmellose natrium dan magnesium stearat
  - cangkang kapsul: gelatin dan titanium dioksida (E171)
  - tinta cetak: shellac, propilen glikol, kalium hidroksida dan black iron oxide (E172).

Seperti apa wujud VILENA dan isi kemasannya

Vilena 2,5 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna putih opak dan tutup kapsul berwarna hijau opak dengan tulisan "L9NL" dan "2.5" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 5 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna putih opak dan tutup kapsul berwarna putih opak dengan tulisan "L9NL" dan "5" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 7,5 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna putih opak dan tutup kapsul berwarna kuning opak dengan tulisan "L9NL" dan "7.5" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 10 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna kuning opak dan tutup kapsul berwarna hijau opak dengan tulisan "L9NL" dan "10" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 15 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna putih opak dan tutup kapsul berwarna biru opak dengan tulisan "L9NL" dan "15" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 20 mg kapsul

Kapsul gelatin keras, dengan badan kapsul berwarna biru opak dan tutup kapsul berwarna hijau opak dengan tulisan "L9NL" dan "20" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Vilena 25 mg kapsul
Kapsul gelatin keras, dengan badan kapsul berwarna putih opak dan tutup kapsul berwarna putih opak dengan tulisan "L9NL" dan "25" dicetak radial pada badan kapsul. Total 21 kapsul per dus.

Nomor Ijin Edar

VILENA 2,5 : DKI2043400701A1
VILENA 5 : DKI2043400701B1
VILENA 7,5 : DKI2043400701C1
VILENA 10 : DKI2043400701D1
VILENA 15 : DKI2043400701E1
VILENA 20 : DKI2043400701F1
VILENA 25 : DKI2043400701G1

HARUS DENGAN RESEP DOKTER

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Di-*release* oleh:
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Diimpor oleh :
PT. Pratapa Nirmala, Tangerang - Indonesia