To be sold by retail on prescription of an Oncologist/Cancer Hospital/ Institution only.

LENATIZ 2.5/5/7.5/10/15/20/25 mg

Lenalidomide Hard Capsules 2.5/5/7.5/10/15/20/25 mg

R_x only

COMPOSITION

LENATIZ 2.5
Lenalidomide Hard Capsules 2.5 mg
Each Hard Capsule contains:
Lenalidomide 2.5 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

LENATIZ 5
Lenalidomide Hard Capsules 5 mg
Each Hard Capsule contains:
Lenalidomide 5 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

LENATIZ 7.5
Lenalidomide Hard Capsules 7.5 mg
Each Hard Capsule contains:
Lenalidomide 7.5 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

LENATIZ 10
Lenalidomide Hard Capsules 10 mg
Each Hard Capsule contains:
Lenalidomide 10 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

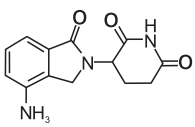
LENATIZ 15
Lenalidomide Hard Capsules 15 mg
Each Hard Capsule contains:
Lenalidomide 15 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

LENATIZ 20
Lenalidomide Hard Capsules 20 mg
Each Hard Capsule contains:
Lenalidomide 20 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

LENATIZ 25
Lenalidomide Hard Capsules 25 mg
Each Hard Capsule contains:
Lenalidomide 25 mg
Excipients q.s.
Colours: Approved colours used in capsule shell.

DESCRIPTION:

Lenalidomide is an analogue of thalidomide. It is an immunomodulatory agent with anti-angiogenic and anti-neoplastic properties. The chemical names is 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure: The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$ and the gram molecular weight is 259.3. Lenolidomide is an off-white to pale-yellow spowder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5mg/ml.



Clinical Pharmacology

Mechanism of Action: 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 haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.

Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma 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 and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.

The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicularlymphoma cells.

Pharmacokinetics: 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 and Distribution: 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 (Cmax) 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.

Distribution

In vitro (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.

14 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.

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.

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.

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 Programmed 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.

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

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following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or uring 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.

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 at least 7 days following discontinuation of lenalidomide. Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule

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). The risk of venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

Overdosage
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). The risk of venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

Dosage And Administration

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.
Follicular lymphoma
For follicular lymphoma patients treated with lenalidomide in combination with rituximab, the overall rate of adverse events is similar for patients aged 65 years or over compared with patients under 65 years of age.
No overall difference in efficacy was observed between the two age groups.
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, myelodys plastic syndromes, mantle cell lymphoma, or follicular 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 3 trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).
Multiple myeloma

Renal function (CLcr)	Dose adjustment
Moderate renal impairment (30 CLcr < 50 mL/min)	10 mg once daily [1]
Moderate renal impairment (30 CLcr < 50 mL/min)	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.

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*	5 mg once daily (days 1 to 21 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 every other day (days 1 to 28 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 every other day (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.

Storage
This medicinal product does not require any special storage conditions.

Shelf Life
2 years

HOW SUPPLIED
HDPE Pack
30 Capsules packed in a HDPE container.

MANUFACTURED & MARKETED BY:
Tizig Pharma Private Limited
Maligoan, Ward no # 5, Kathmandu.
Factory Ward no #1, Banepa, Nepal.