

Dr. Reddy's Laboratories (Pty) Ltd.
EVEROLIMUS 2,5 / 5 / 10 DRL
APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EVEROLIMUS 2,5 DRL, Tablets

EVEROLIMUS 5 DRL, Tablets

EVEROLIMUS 10 DRL, Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EVEROLIMUS 2,5 DRL:

Each tablet contains 2,5 mg everolimus.

Each tablet contains 51,825 mg lactose.

EVEROLIMUS 5 DRL:

Each tablet contains 5 mg everolimus.

Each tablet contains 103,65 mg lactose.

EVEROLIMUS 10 DRL:

Each tablet contains 10 mg everolimus.

Each tablet contains 207,300 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

EVEROLIMUS 2,5 DRL: White to off-white with speckles, elongated tablets with bevelled edge, debossed with '1' on one side and plain on the other side, free from physical defects.

EVEROLIMUS 5 DRL: White to off-white with speckles, elongated tablets with bevelled edge, debossed with '2' on one side and plain on the other side, free from physical defects.

EVEROLIMUS 10 DRL: White to off-white with speckles, elongated tablets with bevelled edge, debossed with '4' on one side and plain on the other side free from physical defects.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma

EVEROLIMUS DRL is indicated for the palliative treatment of patients with advanced renal cell carcinoma, who failed prior treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFTR-TKI) therapy.

4.2 Posology and method of administration

Posology

Treatment with EVEROLIMUS DRL should be initiated by a medical practitioner experienced in the use of anticancer therapies. Treatment should continue as long as clinical benefit is observed or until-unacceptable toxicity occurs.

General target population

Adults:

The recommended dose of EVEROLIMUS DRL for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily.

Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of EVEROLIMUS DRL therapy. If dose reduction is required, the suggested dose is 5 mg daily (see section 4.4).

Moderate CYP3A4 or PgP inhibitors:

Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, the dose should be reduced to 5 mg daily. Further dose reduction to 5 mg every other day may be required to manage adverse reactions (see section 4.4 and 4.5).

If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) should be allowed before the EVEROLIMUS DRL dose is increased. The EVEROLIMUS DRL dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see sections 4.4 and 4.5).

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Strong CYP3A4 inducers:

Avoid the use of concomitant strong CYP3A4 inducers. If patients require coadministration of a strong CYP3A4 inducer, an EVEROLIMUS DRL dose increase from 10 mg daily up to 20 mg daily should be considered (see section 5.2), using 5 mg increments. This dose of EVEROLIMUS DRL is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the EVEROLIMUS DRL dose should be reduced to the dose used prior to initiation of the strong CYP3A4 inducer (see section 4.4 and 4.5).

Dose adjustment recommendations for specific adverse drug reactions

Table 1 summarises recommendations for dose reduction, interruption, or discontinuation of EVEROLIMUS DRL in the management of ADRs. General management recommendations are also provided as applicable.

Clinical judgement of the treating medical practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

Table 1: EVEROLIMUS DRL dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity ^a	EVEROLIMUS DRL Dose Adjustment ^b and Management Recommendations
Non-infectious interstitial pneumonitis	Grade 1 Asymptomatic, clinical, or diagnostic observations only; intervention not indicated	No dose-adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated, limiting instrumental ADL ^c	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade < 1. Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt treatment until symptoms resolve to

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	Severe symptoms; limiting self-care ADL ^c oxygen indicated	Grade < 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	Discontinue treatment, rule out infection and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0,9 %) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade < 1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade < 1. Re-initiate treatment at 5 mg daily. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl amino benzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste). ^d
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade < 1. Re-initiate treatment at 5 mg daily.

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		Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste). ^d
	Grade 4 Life- threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy
Other non-haematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at 5 mg daily.

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		If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyper-glycaemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 ($<LLN^e - 75,000/mm^3$; $<LLN^e - 75.0 \times 10^9/L$)	No dose adjustment required.
	Grade 2 ($<75,000 - 50,000/mm^3$; $<75.0 - 50.0 \times 10^9/L$)	Temporary dose interruption until recovery to Grade ≤ 1 . Re-initiate treatment at same dose.
	Grade 3 ($<50,000 - 25,000/mm^3$; $<50.0 - 25.0 \times 10^9/L$) OR Grade 4 ($<25,000/mm^3$; $<25.0 \times 10^9/L$)	Temporary dose interruption until recovery to Grade ≤ 1 . Re-initiate treatment at 5 mg daily.
	Grade 4 ($<25,000/mm^3$; $<25.0 \times 10^9/L$)	Discontinue treatment and treat with appropriate medical therapy.
Neutropenia (Neutrophil count	Grade 1 ($<LLN^e - 1,500/mm^3$; $<LLN^e - 1.5$	No dose adjustment required.

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decreased)	x 10 ⁹ /L) OR Grade 2 (<1,500 – 1,000/mm ³ ; <1.5 – 1.0 x 10 ⁹ /L)	
	Grade 3 (<1,000 - 500/mm ³ ; <1.0 - 0.5 x 10 ⁹ /L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at same dose.
	Grade 4 (<500/ mm ³ ; <0.5 x 10 ⁹ /L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3 ANC ^f <1,000/mm ³ with a single temperature of >38.3 °C (101°F) or a sustained temperature of ≥38 °C (100.4°F) for more than one hour.	Temporary dose interruption until recovery to Grade ≤2 and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

^a Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

^b If dose reduction is required, the suggested dose is approximately 50 % lower than the dose previously administered.

^c Activities of daily living (ADL)

^d Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

^e Lower limit of normal (LLN)

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^f *Absolute Neutrophil Count (ANC)*

Special populations

Paediatric population:

EVEROLIMUS DRL is not recommended for use in paediatric cancer patients (aged 0 to 18 years) with advanced renal cell carcinoma.

Elderly patients (≥ 65 years):

No dosage adjustment is required (see section 5).

Patients with renal impairment:

No dosage adjustment is required (see section 5).

Patients with hepatic impairment:

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population (see section 4.4 and 5).

Method of administration

EVEROLIMUS DRL should be administered orally once daily at the same time every day, either with or without food. EVEROLIMUS DRL tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

4.3 Contraindications

- Hypersensitivity to everolimus, to other rapamycin derivatives or to any of the excipients listed in (See section 6.1).
- Concomitant use of live vaccines.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported in patients taking everolimus as in EVEROLIMUS DRL (see section 4.8). Some cases were severe and on occasions, a fatal outcome was observed.

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A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as *pneumocystis jirovecii* (*carinii*) pneumonia (PJP/PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see "Infections" below). Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue EVEROLIMUS DRL therapy without dose adjustments. If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP/PCP may be considered. The development of pneumonitis has been reported at a reduced dose.

Infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or PJP/PCP and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) and occasionally fatal outcome.

Medical practitioners and patients should be aware of the increased risk of infection with EVEROLIMUS DRL. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with EVEROLIMUS DRL. While taking EVEROLIMUS DRL, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of EVEROLIMUS DRL.

If a diagnosis of invasive systemic fungal infection is made, the EVEROLIMUS DRL treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

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Cases of PJP/PCP, some with fatal outcome, have been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g., ramipril) therapy may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Stomatitis

Stomatitis, including mouth ulcerations and oral mucositis, is the most commonly reported adverse reaction in patients treated with everolimus as in, EVEROLIMUS DRL (see section 4.8). Stomatitis mostly occurs within the first 8 weeks of treatment. A single-arm study in postmenopausal breast cancer patients treated with everolimus plus exemestane suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment, may decrease the incidence and severity of stomatitis (see section 5.1).

Management of stomatitis may therefore include prophylactic and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash.

However, products containing alcohol, hydrogen peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medicinal products. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5).

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus (see section 4.8). Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

Laboratory tests and monitoring

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Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of EVEROLIMUS DRL therapy and periodically thereafter.

Blood glucose

Hyperglycaemia has been reported (see section 4.8). Monitoring of fasting serum glucose is recommended prior to the start of EVEROLIMUS DRL therapy and periodically thereafter. More frequent monitoring is recommended when EVEROLIMUS DRL is co-administered with other medicinal products that may induce hyperglycaemia. When possible optimal glycaemic control should be achieved before starting a patient on EVEROLIMUS DRL.

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of EVEROLIMUS DRL therapy and periodically thereafter, as well as management with appropriate medical therapy, is recommended.

Haematological parameters

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported (see section 4.8). Monitoring of complete blood count is recommended prior to the start of EVEROLIMUS DRL therapy and periodically thereafter.

Functional carcinoid tumours

In a randomised, double-blind, multi-centre trial in patients with functional carcinoid tumours, everolimus plus depot octreotide was compared to placebo plus depot octreotide. The study did not meet the primary efficacy endpoint (Progression-free-survival [PFS]) and the overall survival (OS) interim analysis numerically favoured the placebo plus depot octreotide arm. Therefore, the safety and efficacy of everolimus in patients with functional carcinoid tumours have not been established.

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of EVEROLIMUS DRL can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with potent CYP3A4 inhibitors results in dramatically increased plasma concentrations of

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everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation.

Hence, concomitant treatment of EVEROLIMUS DRL and potent inhibitors is not recommended.

Caution should be exercised when EVEROLIMUS DRL is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for medicine interactions. If EVEROLIMUS DRL is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g., pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section 4.5). Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown. everolimus should not be given to pregnant women and breast-feeding woman.

Hepatic impairment

Exposure to everolimus was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (see section 5.2).

EVEROLIMUS DRL is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.2 and 5.2).

No clinical safety or efficacy data are currently available to support dose adjustment recommendations for the management of adverse reactions in patients with hepatic impairment.

Vaccinations

The use of live vaccines should be avoided during treatment with EVEROLIMUS DRL (see section 4.5). Close contact with those who have received live vaccines should be avoided during treatment with EVEROLIMUS DRL.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Wound healing complications

Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of EVEROLIMUS DRL in the peri-surgical period.

Radiation therapy complications

Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin

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injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered.

4.5 Interaction with other medicines and other forms of interaction

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in table below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations:

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations:

Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Active substance by Interaction	Interaction - Change in Everolimus AUC/C _{max} Geometric mean ratio (observed range)	Recommendations concerning co-administration
Potent CYP3A4/PgP inhibitors		
Ketoconazole	AUC ↑ 15,3 to fold (range 11,2 to 22,5) C _{max} ↑ 4,1 to fold (range 2,6 to 7,0)	Concomitant treatment of EVEROLIMUS DRL and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		

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Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		
Erythromycin	AUC ↑ 4,4 to fold (range 2,0 to 12,6) C _{max} ↑ 2,0 to fold (range 0,9 to 3,5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the EVEROLIMUS DRL dose is returned to the dose used prior to initiation of the co-administration.
Imatinib	AUC ↑ 3,7 to fold C _{max} ↑ 2,2 to fold	
Verapamil	AUC ↑ 3,5 to fold (range 2,2 to 6,3) C _{max} ↑ 2,3 to fold (range 1,3 to 3,8)	
Ciclosporin oral	AUC ↑ 2,7 to fold (range 1,5 to 4,7) C _{max} ↑ 1,8 to fold (range 1,3 to 2,6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
Potent and moderate CYP3A4 inducers		
Rifampicin	AUC ↓ 63 % (range 0 to 80 %) C _{max} ↓ 58 % (range 10 to 70 %)	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an EVEROLIMUS DRL dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following starts of the inducer. This dose of EVEROLIMUS DRL is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, consider a washout
Dexamethasone	Not studied. Decreased exposure expected.	
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.	

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Efavirenz, nevirapine	Not studied. Decreased exposure expected.	period of at least 3 to 5 days (reasonable time for significant enzyme de -induction), before the EVEROLIMUS DRL dose is returned to the dose used prior to initiation of the co-administration.
St John's Wort (<i>Hypericum perforatum</i>)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Medicines whose plasma concentration may be altered by everolimus

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3M and CYP2D6 unlikely. However, inhibition of CYP3M and PgP in the gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe, with everolimus resulted in a 25 % increase in midazolam C_{max} and a 30 % increase in midazolam AUC(o-inf). The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3M substrates is not expected (see section 4.4).

Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1,47.

Co-administration of everolimus and exemestane increased exemestane C_{min} and C_{2h} by 45 % and 64 %, respectively.

However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety. Aprepitant used to treat nausea and vomiting

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g., ramipril) therapy may be at increased risk for angioedema (see

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section 4.4).

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with EVEROLIMUS DRL. The use of live vaccines should be avoided during treatment with EVEROLIMUS DRL (see section 4.4). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guerin), yellow fever, varicella, and TY21a typhoid vaccines.

Radiation treatment

Potential of radiation treatment toxicity has been reported in patients receiving everolimus (see sections 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use an effective method of contraception while receiving EVEROLIMUS DRL, and for up to 8 weeks after ending treatment.

Pregnancy

There are no adequate data from the use of EVEROLIMUS DRL in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown. EVEROLIMUS DRL should not be given to pregnant women.

Breast-feeding

It is not known whether EVEROLIMUS DRL is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking EVEROLIMUS DRL should therefore not breast-feed during treatment and for 2 weeks after the last dose.

Fertility

Both male and female fertility may be compromised by treatment with EVEROLIMUS DRL.

4.7 Effects on ability to drive and use machines

EVEROLIMUS DRL has minor or moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with EVEROLIMUS DRL.

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4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: within each frequency grouping, and listed in the table below.

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Infections ^{a,*}		
Blood and lymphatic system disorders	Anaemia, thrombocytopenia, neutropenia, leukopenia, lymphopenia	Pancytopenia, Pure red cell aplasia	
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders	Anorexia, decreased appetite, hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia		
Psychiatric disorders	Insomnia, anxiety, somnolence		
Nervous system disorders	Dysgeusia, headache	Ageusia	
Eye disorders	Eyelid oedema	Conjunctivitis	

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Cardiac disorders		Congestive cardiac failure	
Vascular disorders	Haemorrhage ^b , hypertension	Flushing, deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Pneumonitis ^c , epistaxis, cough, dyspnoea	Haemoptysis, pulmonary embolism, acute respiratory distress syndrome	
Gastrointestinal disorders	Stomatitis ^d , diarrhoea, nausea, vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia.		
Hepatobiliary disorders	Aspartate aminotransferase increased, alanine aminotransferase increased		
Skin and subcutaneous tissue disorders	Rash, pruritis, dry skin, nail disorders, mild alopecia, acne, erythema, onycholysis, palmar-plantar erythrodysesthesia syndrome, skin exfoliation, skin lesion	Angioedema*	
Musculoskeletal and connective tissue disorders	Arthralgia		
Renal and urinary disorders	Proteinuria*, blood creatinine increased, renal failure*	Increased daytime urination, acute renal failure*.	

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Reproductive system and breast disorders	Menstruation irregular ^e	Amenorrhoea ^{e*} .	
General disorders and administration site conditions	Mucosal inflammation, fatigue, asthenia, oedema peripheral, pyrexia	Non-cardiac chest pain, impaired wound healing.	
Investigations	Weight decreased		
Injury, poisoning and procedural complications			Radiation recall syndrome ^f , potentiation of radiation reaction ^f

* See also subsection "Description of selected adverse reactions"

^a Includes all reactions within the 'infections and infestations' system organ class including pneumonia, urinary tract infection; bronchitis, herpes zoster, sepsis, abscess, and isolated cases of opportunistic infections [e.g., aspergillosis, candidiasis, PJP/PCP and hepatitis B (see also section 4.4)] and viral myocarditis

^b Includes different bleeding events from different sites not listed individually

^c Includes pneumonitis, interstitial lung disease, lung infiltration and pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

^d Includes stomatitis, aphthous stomatitis, mouth and tongue ulceration and glossodynia, glossitis

^e Frequency based upon number of women from 10 to 55 years of age in the pooled data

^f Adverse reaction identified in the post-marketing setting

Elderly Patients

In the safety pooling, 37 % of the everolimus treated patients were ≥ 65 years of age. The number of patients with an adverse reaction leading to discontinuation of the medicinal product was higher in patients ≥ 65 years of age (20 % vs. 13 %). The most common adverse reactions leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnoea.

Reporting of suspected adverse reactions

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

General supportive measures should be initiated in all cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE10

Pharmacological class: A 34 Other: selective immunosuppressive agents,

Mechanism of action

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. Inhibition of mTORC1, by everolimus has been shown to reduce cell proliferation, glycolysis and angiogenesis in solid tumours in vivo, both through direct antitumour cell activity and inhibition of the tumour stromal compartment.

5.2 Pharmacokinetic properties

Absorption

In patients with advanced solid tumours, peak everolimus concentrations (C_{max}) are reached at a median time of 1 hour after daily administration of 5 mg and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose proportional between 5 mg and 10 mg. Everolimus is a substrate and moderate inhibitor of Pgp.

Food effect

In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22 % and the peak plasma concentration C_{max} by 54 %. Light fat meals reduced AUC by 32 % and C_{max} by 42 %. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

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Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17 % to 73 %. Approximately 20 % of the everolimus concentration in whole blood is confined to plasma in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74 % both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, V_d was 191 l for the apparent central compartment and 5171 for the apparent peripheral compartment.

Biotransformation

Everolimus is a substrate of CYP3A4 and P-gP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

Mean oral clearance (CL_F) of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24,5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

No specific excretion studies have been undertaken in cancer patients; however, data are available from the studies in transplant patients. Following the administration of a single dose of radiolabelled everolimus in conjunction with ciclosporin, 80 % of the radioactivity was recovered from the faeces, while 5 % was excreted in the urine. The parent substance was not detected in urine or faeces.

Steady-state pharmacokinetics

After administration of everolimus in patients with advanced solid tumours, steady-state AUC_{0-τ} was dose-proportional over the range of 5 mg to 10 mg daily dose. Steady-state was achieved within 2 weeks. C_{max} is dose-proportional between 5 mg and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between AUC_{0-τ} and pre-dose trough concentration at steady-state.

Special populations

Hepatic impairment

The safety, tolerability and pharmacokinetics of everolimus were evaluated in two single oral dose studies of everolimus tablets in 8 and 34 subjects with impaired hepatic function relative to subjects with normal hepatic

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function.

In the first study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh B) was twice that found in 8 subjects with normal hepatic function.

In the second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1,6 -fold, 3,3 -fold and 3,6 -fold increase in exposure (i.e., AUC_{0-inf}) for subjects with mild (Child-Pugh A), moderate (Child- Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively.

Simulations of multiple dose pharmacokinetics support the dosing recommendations in subjects with hepatic impairment based on their Child-Pugh status.

Based on the results of the two studies, dose adjustment is recommended for patients with hepatic impairment (see sections 4.2 and 4.4).

Renal impairment

In a population pharmacokinetic analysis of 170 patients with advanced solid tumours, no significant influence of creatinine clearance (25 to 178 mL/min) was detected on CUF of everolimus. Post-transplant renal impairment (creatinine clearance range 11 to 107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients.

Elderly patients

In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27 to 85 years) on oral clearance of everolimus was detected.

Ethnicity

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, CUF is on average 20 % higher in black transplant patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated Hydroxytoluene

Crospovidone (Type A, low peroxide)

Hypromellose 2910

Lactose Anhydrous

Lactose Monohydrate

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Magnesium Stearate (vegetable source)
6.2 Incompatibilities
Not applicable
6.3 Shelf life
24 months
6.4 Special precautions for storage
Store at or below 30 °C. Keep blisters in carton until required for use. This medicine does not require any special storage conditions.
6.5 Nature and contents of container
EVEROLIMUS 2,5 / 5 / 10 DRL: <ul style="list-style-type: none">• Cold formable foil and Peelable lid foil Blister pack comprises of Cold Formable Foil (with Dessicant and HDPE as sealent layer) and Aluminium paper backed peelable foil plain (sealable against PE). Pack size: 30, 60 or 90's. Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling
Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.
7. HOLDER OF CERTIFICATE OF REGISTRATION
Dr. Reddy's Laboratories (Pty) Ltd. Block B, 204 Rivonia Road Morningside Sandton

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2057

8. REGISTRATION NUMBER(S)

EVEROLIMUS 2,5 DRL: 56/32.16/1173

EVEROLIMUS 5 DRL: 56/32.16/1174

EVEROLIMUS 10 DRL: 56/32.16/1175

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 August 2025

10. DATE OF REVISION OF TEXT