

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Everolimus Teva 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg everolimus.

Excipient with known effect:

Each tablet contains 74 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oblong, flat, bevelled edge tablets, approximately 10mm long and 4mm wide, marked with “EV” on one side and “2.5” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Neuroendocrine tumours of gastrointestinal or lung origin

Everolimus Teva is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with Everolimus Teva should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Posology

For the different dose regimens, Everolimus Teva is available as 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets.

The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

If a dose is missed, the patient should not take an additional dose, but take the next prescribed dose as usual.

Dose adjustment due to adverse reactions

Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of Everolimus Teva therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily.

Table 1 summarises the dose adjustment recommendations for specific adverse reactions (see also section 4.4).

Table 1 Everolimus Teva dose adjustment recommendations

Adverse reaction	Severity ¹	Everolimus Teva dose adjustment

Non-infectious pneumonitis	Grade 2	Consider interruption of therapy 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 Grade ≤ 1 . Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤ 1 . Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤ 1 . Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤ 1 . Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤ 1 . Re-initiate treatment at 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 . Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Thrombocytopenia	Grade 2 (<75, $\geq 50 \times 10^9/l$)	Temporary dose interruption until recovery to Grade ≤ 1 ($\geq 75 \times 10^9/l$). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50 $\times 10^9/l$)	Temporary dose interruption until recovery to Grade ≤ 1 ($\geq 75 \times 10^9/l$). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 ($\geq 1 \times 10^9/l$)	No dose adjustment required.
	Grade 3 (<1, $\geq 0.5 \times 10^9/l$)	Temporary dose interruption until recovery to Grade ≤ 2 ($\geq 1 \times 10^9/l$). Re-initiate treatment at same dose.
	Grade 4 (<0.5 $\times 10^9/l$)	Temporary dose interruption until recovery to Grade ≤ 2 ($\geq 1 \times 10^9/l$). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤ 2 ($\geq 1.25 \times 10^9/l$) and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.

¹ Grading based on National Cancer Institute (NCI) Common Terminology Criteria for

Adverse Events (CTCAE) v3.0

Special populations*Elderly patients (≥65 years)*

No dose adjustment is required (see section 5.2).

Renal impairment

No dose adjustment is required (see section 5.2).

Hepatic impairment

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily.
- Severe hepatic impairment (Child-Pugh C) – Everolimus Teva is only recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg daily must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see also sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of everolimus in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Everolimus Teva should be administered orally once daily at the same time every day, consistently either with or without food (see section 5.2). Everolimus Teva tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for useNon-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 (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. 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 Teva 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 pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) may be considered.

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 pneumocystis jirovecii (carinii) pneumonia (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.

Physicians and patients should be aware of the increased risk of infection with Everolimus Teva. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Everolimus Teva. While taking Everolimus Teva, 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 Teva.

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

Cases of pneumocystis jirovecii (carinii) pneumonia (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).

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with everolimus (see section 4.8). In such cases topical treatments are recommended, but mouthwashes containing alcohol, peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. 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

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 Teva 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 Teva therapy and periodically thereafter. More frequent monitoring is recommended when Everolimus Teva 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 Teva.

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of Everolimus Teva 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 Teva 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.

Prognostic factors in neuroendocrine tumours of gastrointestinal or lung origin

In patients with non-functional gastrointestinal or lung neuroendocrine tumours and good prognostic baseline factors, e.g. ileum as primary tumour origin and normal chromogranin A values or without bone involvement, an individual benefit-risk assessment should be performed prior to the start of Everolimus Teva therapy. A limited evidence of PFS benefit was reported in the subgroup of patients with ileum as primary tumour origin (see section 5.1).

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 Teva can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with **potent** CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Everolimus Teva and **potent** inhibitors is not recommended.

Caution should be exercised when Everolimus Teva is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Everolimus Teva 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).

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 Teva is only recommended for use in patients with severe hepatic impairment (Child-Pugh C) if the potential benefit outweighs the risk (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 Teva (see section 4.5).

Lactose

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

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 Teva in the peri-surgical period.

4.5 Interaction with other medicinal products 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 2

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.

Table 2 Effects of other active substances on everolimus

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-fold (range 11.2-22.5) C _{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of everolimus and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C _{max} ↑2.0-fold (range 0.9-3.5)	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
Imatinib	AUC ↑ 3.7-fold C _{max} ↑ 2.2-fold	
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C _{max} ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C _{max} ↑1.8-fold (range 1.3-2.6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	

Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	everolimus dose is returned to the dose used prior to initiation of the co-administration.
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 0-80%) C _{max} ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an everolimus 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 start of the inducer. This dose of everolimus 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 period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the co-administration.
Dexamethasone	Not studied. Decreased exposure expected.	
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John’s Wort (<i>Hypericum perforatum</i>)	Not studied. Large decrease in exposure expected.	

Agents 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, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 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(0-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 CYP3A4 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. A clinically significant effect on the efficacy response to everolimus in patients with advanced neuroendocrine tumours could not be established.

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 events 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.

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 section 4.4).

Vaccinations

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment. Male patients should not be prohibited from attempting to father children.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 5.3). The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk (see section 5.3). Therefore, women taking everolimus should not breast-feed.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown, however amenorrhoea (secondary amenorrhoea and other menstrual irregularities) and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus (see section 5.3).

4.7 Effects on ability to drive and use machines

Everolimus Teva may have a 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 Teva.

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 2,672 patients treated with everolimus in ten clinical studies, consisting of five randomised, double-blind, placebo controlled phase III studies and five open-label phase I and phase II studies, related to the approved indications.

The most common adverse reactions (incidence $\geq 1/10$) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, cough and headache.

The most frequent Grade 3-4 adverse reactions (incidence $\geq 1/100$ to $< 1/10$) were stomatitis, anaemia, hyperglycaemia,

infections, fatigue, diarrhoea, pneumonitis, asthenia, thrombocytopenia, neutropenia, dyspnoea, proteinuria, lymphopenia, haemorrhage, hypophosphataemia, rash, hypertension, pneumonia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and diabetes mellitus. The grades follow CTCAE Version 3.0 and 4.03.

Tabulated list of adverse reactions

Table 3 presents the frequency category of adverse reactions reported in the pooled analysis considered for the safety pooling. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions reported in clinical studies

Infections and infestations	
Very common	Infections ^a , *
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Eye disorders	
Common	Eyelid oedema
Uncommon	Conjunctivitis
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage ^b , hypertension
Uncommon	Flushing, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis ^c , epistaxis, cough
Common	Dyspnoea
Uncommon	Haemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis ^d , diarrhoea, nausea
Common	Vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia
Hepatobiliary disorders	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus

Common	Dry skin, nail disorders, mild alopecia, acne, erythema, onychoclasia, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, skin lesion
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria*, blood creatinine increased, renal failure*
Uncommon	Increased daytime urination, acute renal failure*
Reproductive system and breast disorders	
Common	Menstruation irregular ^e
Uncommon	Amenorrhoea ^e
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral
Common	Pyrexia
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
* See also subsection “Description of selected adverse reactions”	
a Includes all reactions within the ‘infections and infestations’ system organ class including (common) pneumonia, urinary tract infection; (uncommon) bronchitis, herpes zoster, sepsis, abscess and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis, pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and hepatitis B (see also section 4.4)] and (rare) viral myocarditis	
b Includes different bleeding events from different sites not listed individually	
c Includes (common) pneumonitis, interstitial lung disease, lung infiltration and (rare) pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis	
d Includes (very common) stomatitis, (common) aphthous stomatitis, mouth and tongue ulceration and (uncommon) glossodynia, glossitis	
e Frequency based upon number of women from 10 to 55 years of age in the pooled data	

Description of selected adverse reactions

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended (see section 4.4).

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities).

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome (see section 4.4).

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see section 4.4).

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

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 via HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. 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

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. S6K1 is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Clinical efficacy and safety

Advanced neuroendocrine tumours of gastrointestinal or lung origin

RADIANT-4 (study CRAD001T2302), a randomised, double-blind, multicentre, phase III study of everolimus plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with advanced, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome.

The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), based on independent radiology assessment. Supportive PFS analysis was based on local investigator review. Secondary endpoints included overall survival (OS), overall response rate, disease control rate, safety, change in quality of life (FACT-G) and time to World Health Organisation performance status (WHO PS) deterioration.

A total of 302 patients were randomised in a 2:1 ratio to receive either everolimus (10 mg daily) (n=205) or placebo (n=97). Demographics and disease characteristics were generally balanced (median age 63 years [range 22 to 86], 76% Caucasian, history of prior somatostatin analogue [SSA] use). The median duration of blinded treatment was 40.4 weeks for patients receiving everolimus and 19.6 weeks for those receiving placebo. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

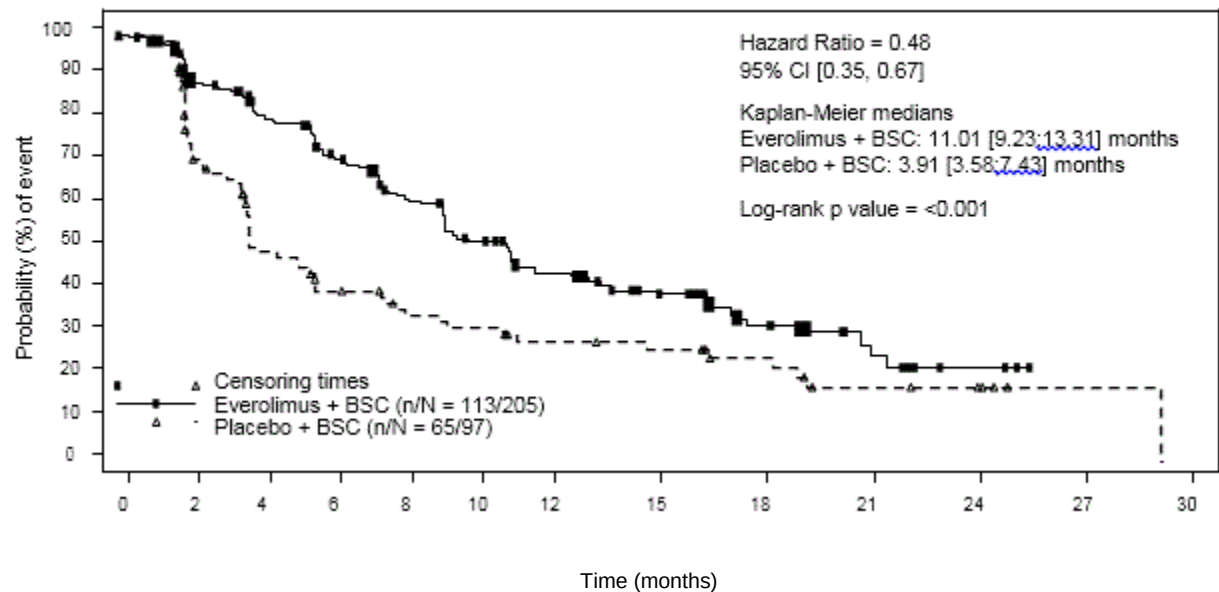
The efficacy results for the primary endpoint were obtained from the final PFS analysis (see Table 6 and Figure 3).

Table 6 RADIANT-4 – Progression-free survival results

Population	Everolimus n=205	Placebo n=97	Hazard ratio (95% CI)	p-value ^a
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Median progression-free survival (months) (95% CI)				
Independent radiological review	11.01 (9.2, 13.3)	3.91 (3.6, 7.4)	0.48 (0.35, 0.67)	<0.0001
Investigator radiological review	13.96 (11.2, 17.7)	5.45 (3.7, 7.4)	0.39 (0.28, 0.54)	<0.0001
^a One-sided p-value from a stratified log-rank test				

Figure 3 RADIANT-4 – Kaplan-Meier progression-free survival curves (independent radiological review)

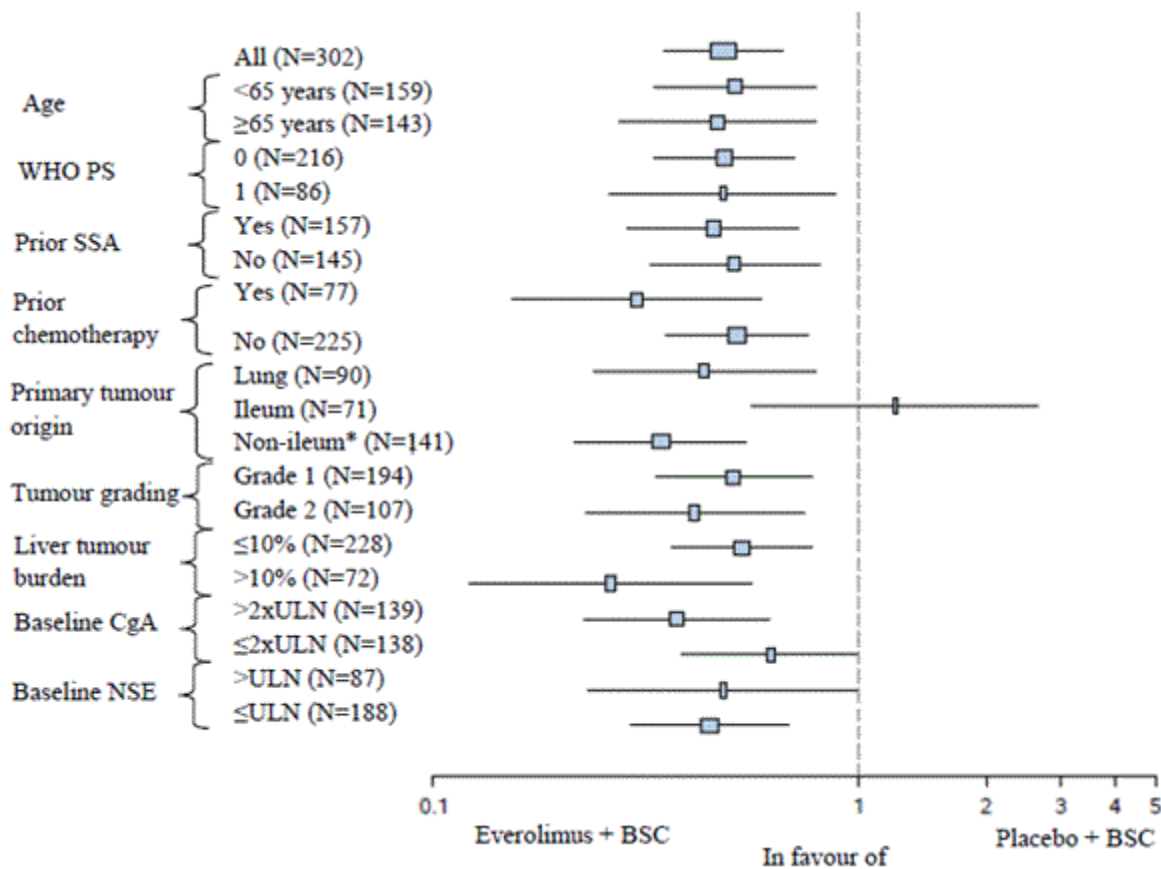


Number of Patients still at Risk

Time (months)	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

In supportive analyses, positive treatment effect has been observed in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]; Non-ileum: HR=0.34 [95% CI: 0.22 to 0.54]; Lung: HR=0.43 [95% CI: 0.24 to 0.79]) (see Figure 4).

Figure 4 RADIANT-4 – Progression free survival results by pre-specified patient subgroup (independent radiological review)



*Non-ileum: stomach, colon, rectum, appendix, caecum, duodenum, jejunum, carcinoma of unknown primary origin and other gastrointestinal origin
ULN: Upper limit of normal
CgA: Chromogranin A
NSE: Neuron specific enolase
Hazard ratio (95% CI) from stratified Cox model

The pre-planned OS interim analysis after 101 deaths (out of 191 required for final analysis) and 33 months follow-up favoured the everolimus arm; however, no statistically significant difference in OS was noted (HR= 0.73 [95% CI: 0.48 to 1.11; p=0.071]).

No difference in the time to definitive deterioration of WHO PS (≥1 point) and time to definitive deterioration in quality of life (FACT-G total score ≥7 points) was observed between the two arms.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product in all subsets of the paediatric population in thoracic neuroendocrine tumours (see section 4.2 for information on paediatric use).

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 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 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.

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 517 l for the apparent peripheral compartment.

Biotransformation

Everolimus is a substrate of CYP3A4 and PgP. 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 $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg daily dose. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ 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 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. $AUC_{0-\infty}$) 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 (25-178 ml/min) was detected on CL/F of everolimus.

Post-transplant renal impairment (creatinine clearance range 11-107 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 (27-85 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, CL/F is on average 20% higher in black transplant patients.

5.3 Preclinical safety data

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; pancreas (degranulation and vacuolation of exocrine cells in monkeys and minipigs, respectively, and degeneration of islet cells in monkeys), and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg which caused a reduction in male fertility. There was evidence of reversibility.

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% of the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss.

Everolimus crossed the placenta and was toxic to the foetus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E321)
 Hypromellose
 Lactose monohydrate
 Lactose anhydrous
 Crospovidone
 Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

OPA/Alu/PVC – Aluminium blisters containing 10, 30, 30x1, 50x1, 60 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/034/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th June 2017

10 DATE OF REVISION OF THE TEXT