SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Everolimus Krka 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg everolimus.

Excipient with known effect

Each tablet contains 295.75mg lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off white oval and biconvex tablets (approximately 16 x 8 mm), debossed with E9VS 10 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone receptor-positive advanced breast cancer

Everolimus Krka is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

Neuroendocrine tumours of pancreatic origin

Everolimus Krka is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Neuroendocrine tumours of gastrointestinal or lung origin

Everolimus Krka 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).

Renal cell carcinoma

Everolimus Krka is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

4.2 Posology and method of administration

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

Posology

For the different dose regimens Everolimus Krka is available as 2.5 mg, 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 Krka 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 Krka dose adjustment recommendations

Adverse reaction	**Severity[1]**	**Everolimus Krka 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, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/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 Krka 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 Krka in children aged 0 to 18 years have not been established. No data are available.

Method of administration
Everolimus Krka should be administered orally once daily at the same time every day, consistently either with or without food (see section 5.2). Everolimus Krka 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 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 Krka (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 Krka 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 Krka. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Everolimus Krka. While taking Everolimus Krka, 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 Krka.

If a diagnosis of invasive systemic fungal infection is made, the Everolimus Krka 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).

Stomatitis

Stomatitis, including mouth ulcerations and oral mucositis is the most commonly reported adverse reaction observed in patients treated with everolimus (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 medications. 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 Krka 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 Krka therapy and periodically thereafter. More frequent monitoring is recommended when Everolimus Krka 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 Krka.

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of Everolimus Krka 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 Krka 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 Krka 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, the clinical condition of the patient should be monitored closely. Dose adjustments of Everolimus Krka can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with ***potent*** CYP3A4/PgP 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 Krka and ***potent*** inhibitors is not recommended.

Caution should be exercised when Everolimus Krka is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Everolimus Krka 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 Krka 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 Krka (see section 4.5).

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 Krka in the peri-surgical period.

Radiation therapy complications
Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin 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.

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

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 Krka 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 (see sections 4.2 and 4.4). 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 Krka dose is returned to the dose used prior to initiation of the
Imatinib	AUC ↑ 3.7-fold C_{max} **t** 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)	
Cannabidiol (P-gp inhibitor)	AUC↑2.5-fold C_{max} ↑2.5-fold	
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 0-80%) 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 Krka 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 Krka 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 Krka 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 (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

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 $AUC_{(0\text{-}inf)}$,. 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 Krka. The use of live vaccines should be avoided during treatment with Everolimus Krka (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.

Radiation treatment

Potentiation 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/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 human 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 during treatment and for 2 weeks after the last dose..

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 Krka 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 Krka.

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 2,879 patients treated with everolimus in eleven clinical studies, consisting of five randomised, double-blind, placebo controlled phase III studies and six open-label phase I and phase II studies, related to the approved indications.

The most common adverse reactions (incidence ≥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 ≥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); not known (cannot be estimated from the available data). 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, lymphoedema[g]
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, onychoclasis, 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
Injury, poisoning and procedural complications	
Not known[f]	Radiation recall syndrome, potentiation of radiation reaction

* 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 (very common) pneumonitis, (common) 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

[f] Adverse reaction identified in the post-marketing setting

[g] Adverse reaction was determined based on post-marketing reports. Frequency was determined based on oncology studies safety pool.

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 Yellow Card Scheme, Website: yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, protein kinase inhibitors, ATC code: L01EG02

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. S6K1is 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

Hormone receptor-positive advanced breast cancer

BOLERO-2 (study CRAD001Y2301), a randomised, double-blind, multicentre phase III study of Everolimus + exemestane versus placebo + exemestane, was conducted in postmenopausal women with oestrogen receptor-positive, HER2/neu negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomisation was stratified by documented sensitivity to

prior hormonal therapy and by the presence of visceral metastasis. Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥24 weeks) from at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

The primary endpoint for the study was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumours), based on the investigator's assessment (local radiology). Supportive PFS analyses were based on an independent central radiology review.

Secondary endpoints included overall survival (OS), objective response rate, clinical benefit rate, safety, change in quality of life (QoL) and time to ECOG PS (Eastern Cooperative Oncology Group performance status) deterioration.

A total of 724 patients were randomised in a 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n=485) or to the placebo + exemestane arm (25 mg daily) (n=239). At the time of the final OS analysis, the median duration of everolimus treatment was 24.0 weeks (range 1.0-199.1 weeks). The median duration of exemestane treatment was longer in the everolimus + exemestane group at 29.5 weeks (1.0-199.1) compared to 14.1 weeks (1.0-156.0) in the placebo + exemestane group.

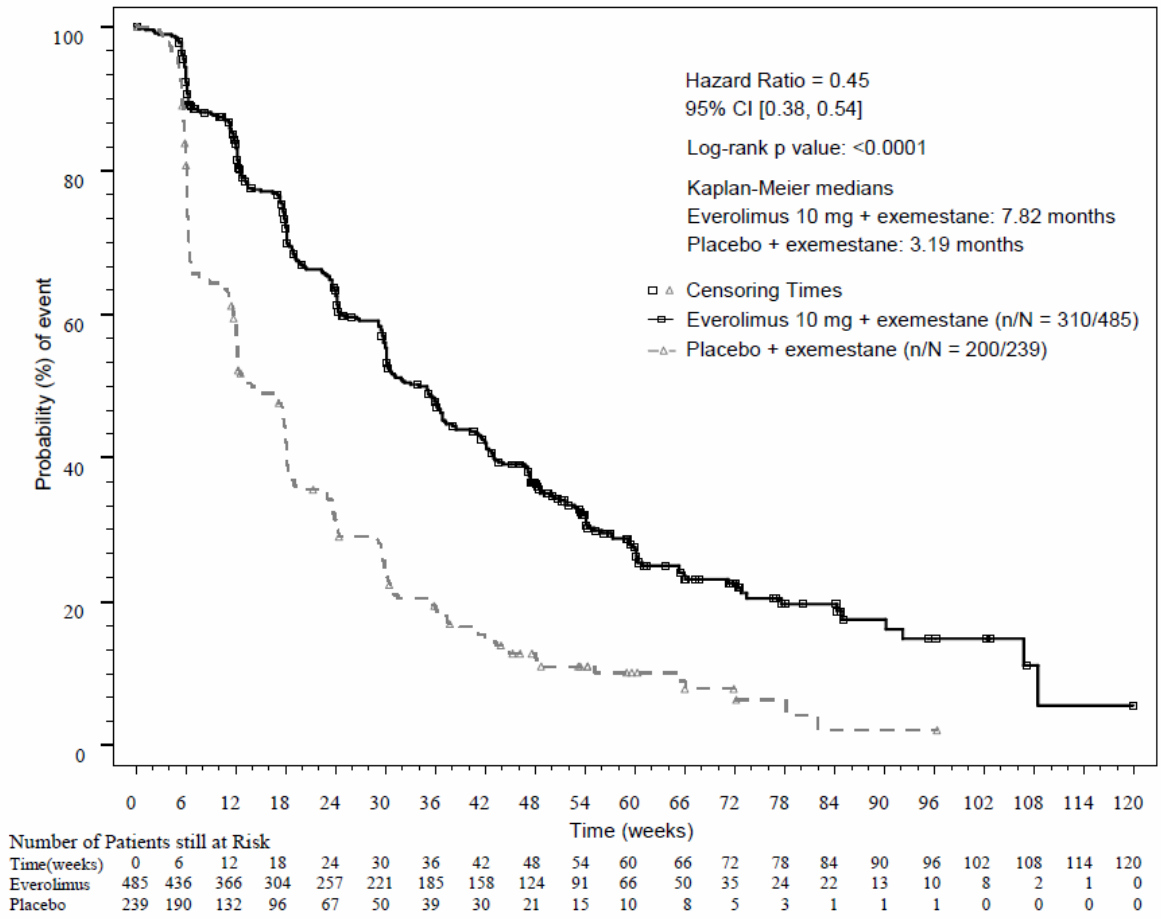
The efficacy results for the primary endpoint were obtained from the final PFS analysis (see Table 4 and Figure 1). Patients in the placebo + exemestane arm did not cross over to everolimus at the time of progression.

Table 4 BOLERO-2 efficacy results

Analysis	**Everolimus[a] n=485**	**Placebo[a] n=239**	**Hazard ratio**	**p value**
Median progression-free survival (months) (95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38 (0.31 to 0.48)	<0.0001
Median overall survival (months) (95% CI)				
Median overall survival	31.0 (28.0 - 34.6)	26.6 (22.6 - 33.1)	0.89 (0.73 - 1.10)	0.1426
Best overall response (%) (95% CI)				
Objective response rate[b]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[d]	<0.0001[e]
Clinical benefit rate[c]	51.3% (46.8 to 55.9)	26.4% (20.9 to 32.4)	n/a[d]	<0.0001[e]

[a] Plus exemestane
[b] Objective response rate = proportion of patients with complete or partial response
[c] Clinical benefit rate = proportion of patients with complete or partial response or stable disease ≥24 weeks
[d] Not applicable
[e] p value is obtained from the exact Cochran-Mantel-Haenszel test using a stratified version of the Cochran-Armitage permutation test.

Figure 1 BOLERO-2 Kaplan-Meier progression-free survival curves (investigator radiological review)



The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analysed subgroups (age, sensitivity to prior hormonal therapy, number of organs involved, status of bone-only lesions at baseline and presence of visceral metastasis, and across major demographic and prognostic subgroups) a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio (HR) versus placebo + exemestane ranging from 0.25 to 0.60.

No differences in the time to ≥5% deterioration in the global and functional domain scores of QLQ-C30 were observed in the two arms.

BOLERO-6 (Study CRAD001Y2201), a three-arm, randomised, open-label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor-positive, HER2/neu negative, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole.

The primary objective of the study was to estimate the HR of PFS for everolimus + exemestane versus everolimus alone. The key secondary objective was to estimate the HR of PFS for everolimus + exemestane versus capecitabine.

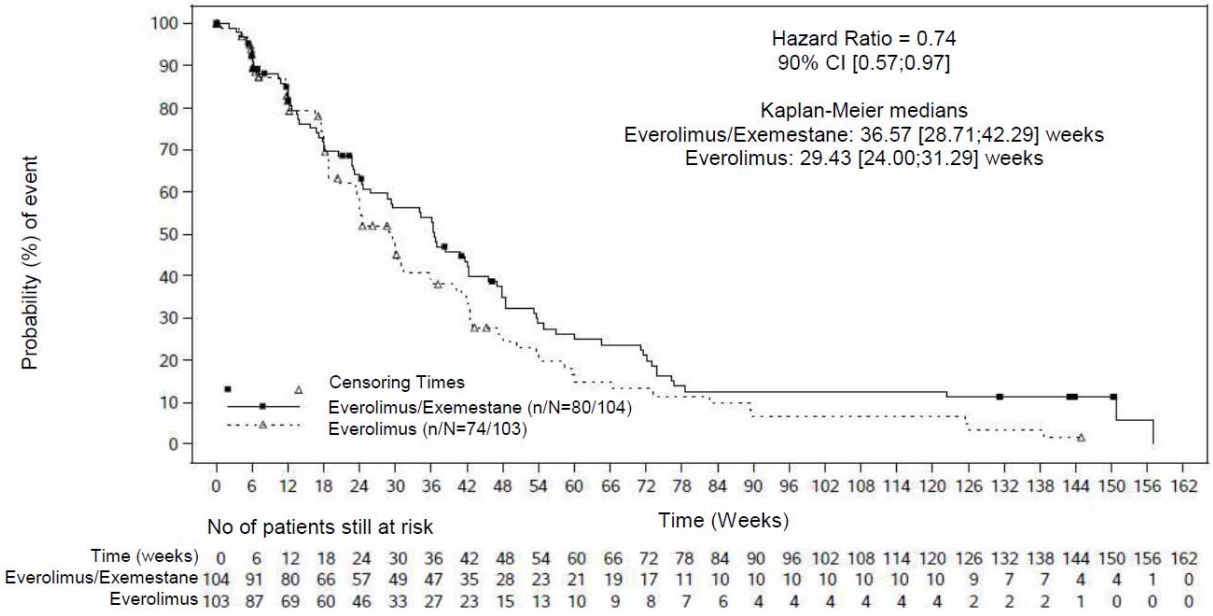
Other secondary objectives included the evaluation of OS, objective response rate, clinical benefit rate, safety, time to ECOG performance deterioration, time to QoL

deterioration, and treatment satisfaction (TSQM). No formal statistical comparisons were planned.

A total of 309 patients were randomised in a 1:1:1 ratio to the combination of everolimus (10 mg daily) + exemestane (25 mg daily) (n=104), everolimus alone (10 mg daily) (n=103), or capecitabine (1250 mg/m2 dose twice daily for 2 weeks followed by one week rest, 3-week cycle) (n=102). At the time of data cut-off, the median duration of treatment was 27.5 weeks (range 2.0-165.7) in the everolimus + exemestane arm, 20 weeks (1.3-145.0) in the everolimus arm, and 26.7 weeks (1.4-177.1) in the capecitabine arm.

The result of the final PFS analysis with 154 PFS events observed based on local investigator assessment showed an estimated HR of 0.74 (90% CI: 0.57, 0.97) in favour of the everolimus + exemestane arm relative to everolimus arm. The median PFS was 8.4 months (90% CI: 6.6, 9.7) and 6.8 months (90% CI: 5.5, 7.2), respectively.

Figure 2 BOLERO-6 Kaplan-Meier progression-free survival curves (investigator radiological review)



For the key secondary endpoint PFS the estimated HR was 1.26 (90% CI: 0.96, 1.66) in favour of capecitabine over the everolimus + exemestane combination arm based on a total of 148 PFS events observed.

Results of the secondary endpoint OS were not consistent with the primary endpoint PFS, with a trend observed favouring the everolimus alone arm. The estimated HR was 1.27 (90% CI: 0.95, 1.70) for the comparison of OS in the everolimus alone arm relative to the everolimus + exemestane arm. The estimated HR for the comparison of OS in the everolimus + exemestane combination arm relative to capecitabine arm was 1.33 (90% CI: 0.99, 1.79).

Advanced neuroendocrine tumours of pancreatic origin (pNET)

RADIANT-3 (study CRAD001C2324), a phase III, multicentre, randomised, double-blind study of everolimus plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pNET, demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.4-fold prolongation of median progression-free-survival (PFS) (11.04 months versus 4.6 months), (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 5 and Figure 3).

RADIANT-3 involved patients with well- and moderately-differentiated advanced pNET whose disease had progressed within the prior 12 months. Treatment with somatostatin analogues was allowed as part of BSC.

The primary endpoint for the study was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumours). Following documented radiological progression, patients could be unblinded by the investigator. Those randomised to placebo were then able to receive open-label everolimus.

Secondary endpoints included safety, objective response rate, response duration and overall survival (OS).

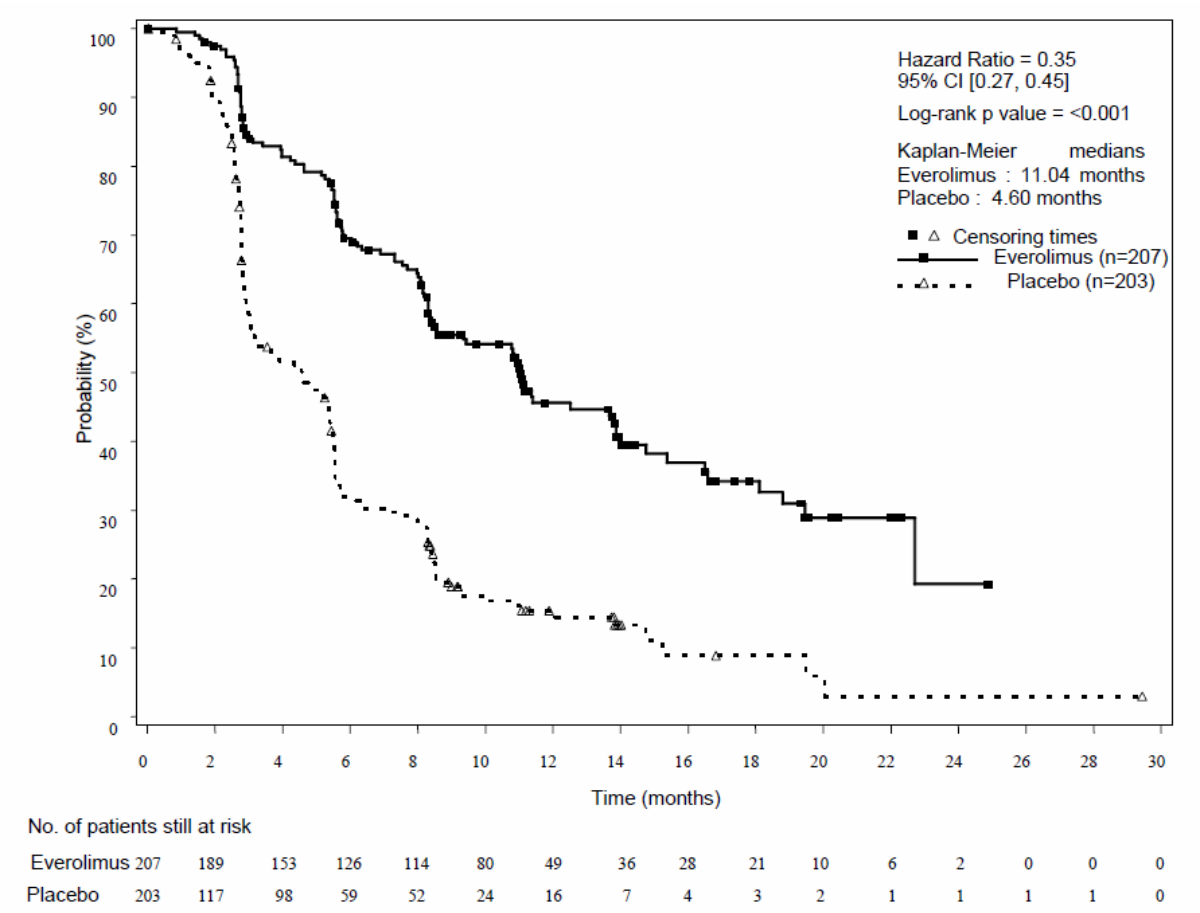
In total, 410 patients were randomised 1:1 to receive either everolimus 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 78.5% Caucasian). Fifty-eight percent of the patients in both arms received prior systemic therapy. The median duration of blinded study treatment was 37.8 weeks (range 1.1-129.9 weeks) for patients receiving everolimus and 16.1 weeks (range 0.4-147.0 weeks) for those receiving placebo.

Following disease progression or after study unblinding, 172 of the 203 patients (84.7%) initially randomised to placebo crossed over to open-label everolimus. The median duration of open-label treatment was 47.7 weeks among all patients; 67.1 weeks in the 53 patients randomised to everolimus who switched to open-label everolimus and 44.1 weeks in the 172 patients randomised to placebo who switched to open-label everolimus.

Table 5 RADIANT-3 - efficacy results

Population	**Everolimus n=207**	**Placebo n=203**	**Hazard ratio (95% CI)**	**p-value**
Median progression-free survival (months) (95% CI)				
Investigator radiological review	11.04 (8.41, 13.86)	4.60 (3.06, 5.39)	0.35 (0.27, 0.45)	<0.0001
Independent radiological review	13.67 (11.17, 18.79)	5.68 (5.39, 8.31)	0.38 (0.28, 0.51)	<0.0001
Median overall survival (months) (95% CI)				
Median overall survival	44.02 (35.61, 51.75)	37.68 (29.14, 45.77)	0.94 (0.73, 1.20)	0.300

Figure 3 **RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)**



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 Tumours (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. After primary PFS analysis, 6 patients from the placebo arm crossed over to open-label everolimus.

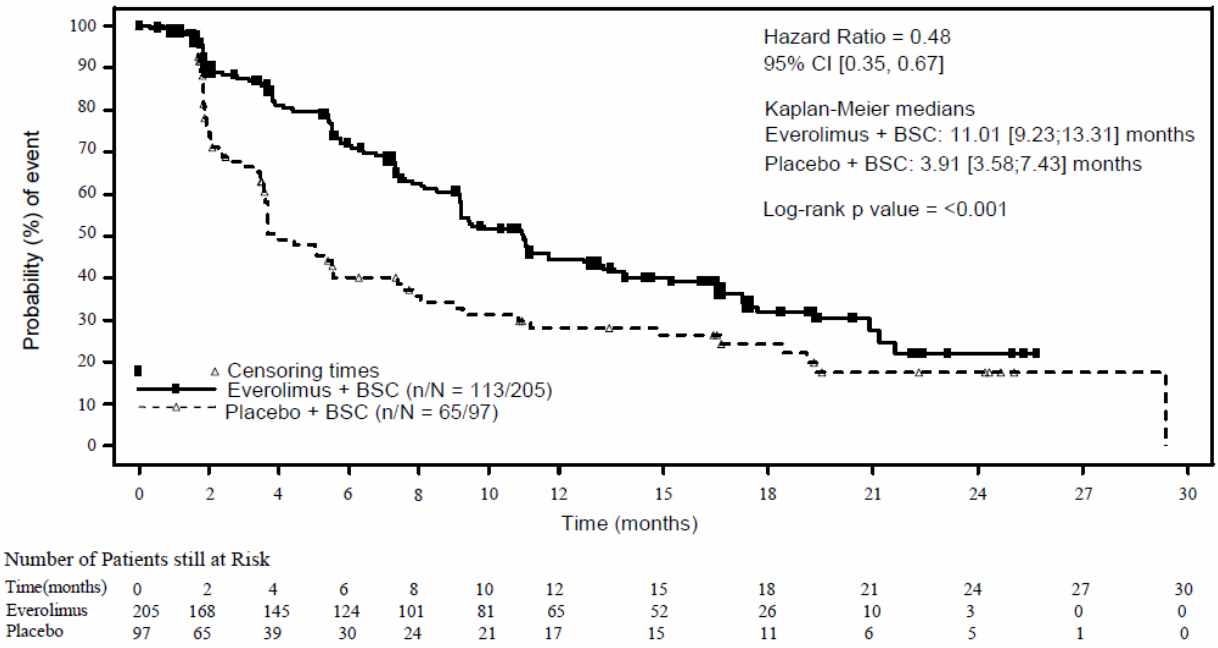
The efficacy results for the primary endpoint PFS (independent radiological review) were obtained from the final PFS analysis (See Table 6 and Figure 4). The efficacy

results for PFS (investigator radiological review) were obtained from the final OS analysis (see Table 6).

Table 6 RADIANT-4 – Progression-free survival results

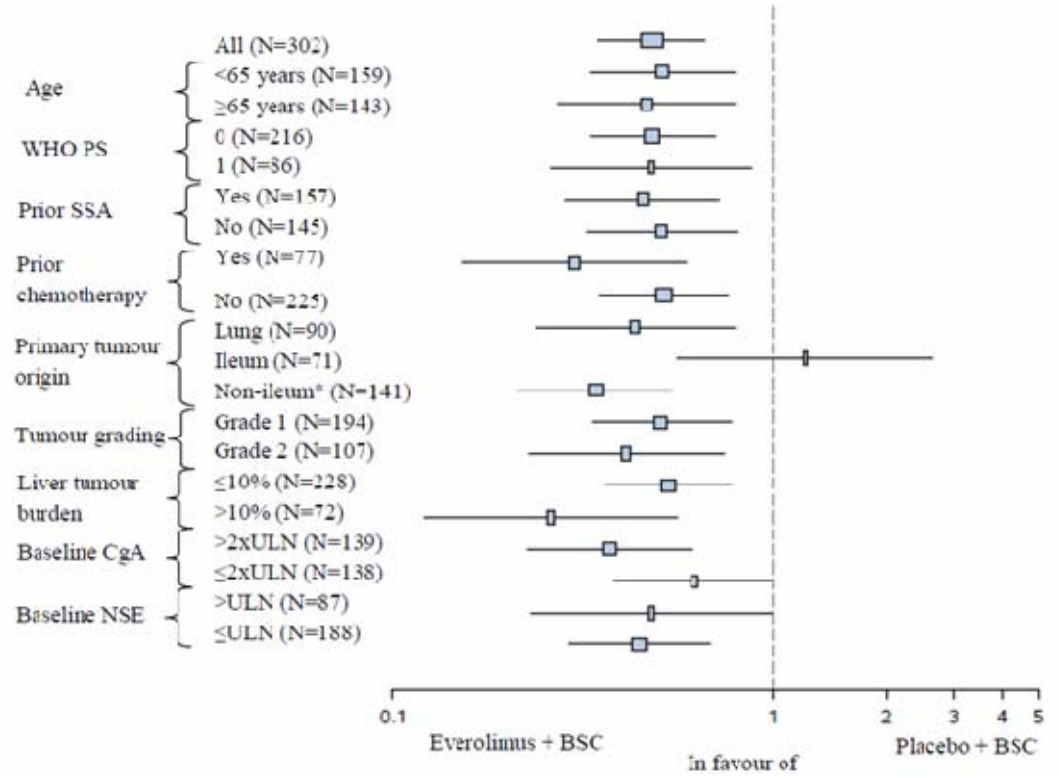
Population	Everolimus n=205	Placebo n=97	Hazard ratio (95% CI)	p-value[a]
Median progression-free survival (months) (95% CI)				
Independent radiological review	11.01 (9.2, 13.3)	3.91 (3.6, 7.4)	0.48 (0.35, 0.67)	<0.001
Investigator radiological review	14.39 (11.24, 17.97)	5.45 (3.71, 7.39)	0.40 (0.29, 0.55)	<0.001
[a] One-sided p-value from a stratified log-rank test				

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



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 5).

Figure 5 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 final overall survival (OS) analysis did not show a statistically significant difference between those patients who received everolimus or placebo during the blinded treatment period of the study (HR=0.90 [95% CI: 0.66 to 1.22]).

No difference in the time to definitive deterioration of WHO PS (HR=1.02; [95% CI: 0.65, 1.61]) and time to definitive deterioration in quality of life (FACT-G total score HR=0.74; [95% CI: 0.50, 1.10]) was observed between the two arms.

Advanced renal cell carcinoma

RECORD-1 (study CRAD001C2240), a phase III, international, multicentre, randomised, double-blind study comparing everolimus 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed on or after treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-α was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- *vs.* intermediate- *vs.* poor-risk groups) and prior anticancer therapy (1 *vs.* 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response

rate, overall survival, disease-related symptoms, and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label everolimus 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomised 2:1 to receive everolimus (n=277) or placebo (n=139). Demographics were well balanced (pooled median age [61 years; range 27-85], 78% male, 88% Caucasian, number of prior VEGFR-TKI therapies [1-74%, 2-26%]). The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving everolimus and 60 days (range 21-295 days) for those receiving placebo.

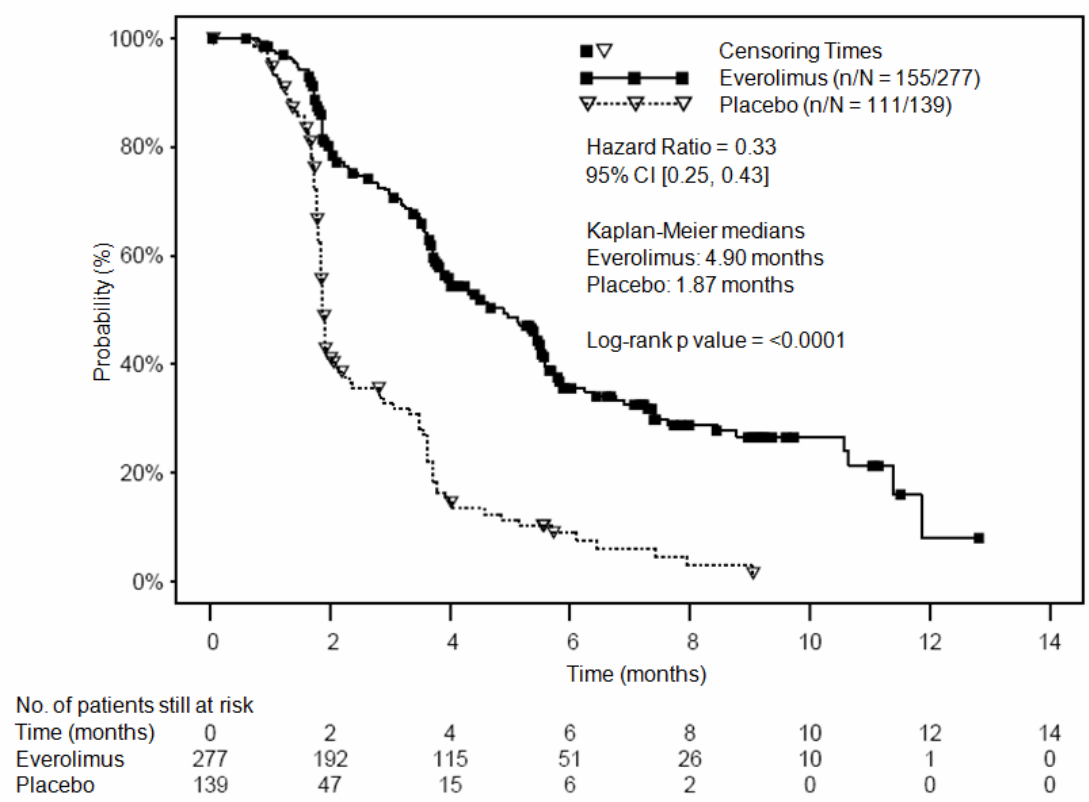
Everolimus was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 7 and Figure 6).

Table 7 RECORD-1 - Progression-free survival results

Population	**n**	**Everolimus n=277**	**Placebo n=139**	**Hazard ratio (95%CI)**	**p-value**
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0-5.5)	1.9 (1.8-1.9)	0.33 (0.25-0.43)	<0.0001[a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6-5.8)	1.9 (1.8-2.2)	0.32 (0.25-0.41)	<0.0001[a]
MSKCC prognostic score (blinded independent central review)					
Favourable risk	120	5.8 (4.0-7.4)	1.9 (1.9-2.8)	0.31 (0.19-0.50)	<0.0001
Intermediate risk	235	4.5 (3.8-5.5)	1.8 (1.8-1.9)	0.32 (0.22-0.44)	<0.0001
Poor risk	61	3.6 (1.9-4.6)	1.8 (1.8-3.6)	0.44 (0.22-0.85)	0.007

[a] Stratified log-rank test

Figure 6 RECORD-1 – Kaplan-Meier progression-free survival curves (independent central review)



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14
Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

Six-month PFS rates were 36% for everolimus therapy compared with 9% for placebo.

Confirmed objective tumour responses were observed in 5 patients (2%) receiving everolimus, while none were observed in patients receiving placebo. Therefore, the progression-free survival advantage primarily reflects the population with disease stabilisation (corresponding to 67% of the everolimus treatment group).

No statistically significant treatment-related difference in overall survival was noted (hazard ratio 0.87; confidence interval: 0.65-1.17; p=0.177). Crossover to open-label everolimus following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

Other studies

Stomatitis is the most commonly reported adverse reaction in patients treated with everolimus (see sections 4.4 and 4.8). In a post-marketing single-arm study in postmenopausal women with advanced breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 ml alcohol-free oral solution was administered as a mouthwash (4 times daily for the initial 8 weeks of treatment) to patients at the time of initiating treatment with everolimus (10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. The incidence of Grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported. The incidence of Grade 1 stomatitis was 18.8% (n=16/85) and no cases of Grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus in the oncology and tuberous sclerosis complex (TSC) settings, with the exception of a slightly increased frequency of oral candidiasis which was reported in 2.2% (n=2/92) of patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing everolimus in all subsets of the paediatric population in neuroendocrine tumours of pancreatic origin, thoracic neuroendocrine tumours and in renal cell carcinoma (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-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 (25-178 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 $AUC_{0\text{-}24h}$ 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 (E464)
Lactose
Lactose monohydrate
Crospovidone (E1202)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

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/Al/PVC/Al blister

Everolimus Krka 10 mg is available in packs containing 10, 30 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/05/2023

10 DATE OF REVISION OF THE TEXT

26/02/2024