NOVARTIS

Patient Safety & Pharmacovigilance

Everolimus

RAD001

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Everolimus
Product(s) concerned (brand name(s)):	Afinitor® and Votubia®
Document status:	Final
Version number:	16.0/16.0
Data lock point for this RMP	PSUR Afinitor; 31-Mar-2024 PSUR Votubia; 31-Mar-2024
Date of final sign off	31-May-2024

Rationale for submitting an updated RMP: The Risk Management Plan, EU RMP v16.0/16.0, is prepared to reflect the completion of study CRAD001M2305 for Votubia. The RMP is also aligned with the Final Assessment Report of the EU RMP v15.0/15.0 issued from PRAC procedure No. EMEA/H/C/WS1923.

Summary of significant changes in this RMP:

Compared to EU RMP v15.0/15.0 (dated 29-Jun-2020), this version has been updated to reflect:

- Removal of safety concerns "Male infertility" (TSC setting only) and "Female infertility" (TSC setting only) as recommended by PRAC in the Final Assessment Report Afinitor/Votubia RMP v15.0/15.0 (procedure No. EMEA/H/C/WS1923).
- Completion of the additional PV activity, study CRAD001M2305.
- Removal of safety concerns "Postnatal developmental toxicity (TSC setting only), "Long-term safety" (TSC setting only) and "Neurocognitive and sexual development in pediatric patients" (TSC setting only) as study CRAD001M2305 is now completed.
- The RMP is also aligned with new RMP template version 6.4 and updated with exposure data from latest PSURs for Afinitor and Votubia with DLP; 31-Mar-2024.

Part	Major changes compared to RMP v15.0/v15.0
Part I	No update
Part II	Module SIII and SV: Updated exposure tables Module SVII.2: Removal of important identified risks, important potential risks and missing information Updated the clinical trial and post marketing exposure.
Part III	Removal of checklists and additional pharmacovigilance activities
Part IV	No update
Part V	Removal of risks minimization errors as no risks identified
Part VI	Removal of summary of risks listed in Part II
Part VII	**Annex 4**: Removed all the targeted follow-up checklists **Annex 6**: No update

Other RMP versions under evaluation: No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: Afinitor v15.0 / Votubia v15.0

Approved with procedure: EMEA/H/C/WS1671

Date of approval (opinion date): 29-Oct-2020

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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Not Applicable

List of abbreviations

ADR	Adverse Drug Reaction
CYP	Cytochromes 450
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HA	Health Authority
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NET	Neuroendocrine tumors
PRAC	Pharmacovigilance Risk Assessment Committee
PBRER	Periodic benefit-risk evaluation report
SOC	System organ class
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TOR	Target of Rapamysin
TSC	Tuberous Sclerosis Complex

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Everolimus
Pharmacotherapeutic group(s) (ATC Code)	L01XE10
Marketing Authorization Holder	Novartis Europharm Limited.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Afinitor®, Votubia®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class:** Rapamycin derivative or mammalian target of rapamycin (mTOR) inhibitor
	Summary of mode of action: Selective mTOR inhibitor, specifically targeting the mTOR-raptor signal transduction complex (mTORC1), which is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway
	Important information about its composition: As everolimus is not a vaccine or biologic derivate, this is not applicable
Hyperlink to the Product Information	[Current approved Afinitor SmPC] [Current approved Votubia SmPC]
Indications in the EEA	**Afinitor** **Current:** Afinitor (everolimus) is indicated for the treatment of adult patients with: (1) advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy [RCC]; (2) unresectable or metastatic, well- or moderately differentiated neuroendocrine tumors (NET) of pancreatic origin in adults with progressive disease [pNET]; (3) 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 [BREAST]; and (4) unresectable or metastatic, well differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumors (NET) of gastrointestinal or lung origin in adults with progressive disease. **Votubia** Current: Votubia (everolimus) is indicated: (5) for the treatment of pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated [TSC-SEGA]; (6) for the treatment of adult patients with renal angiomyolipoma

	associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume [TSC-AML]; and (7) as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC [TSC-Seizures].
	Proposed: Not applicable
Dosage in the EEA	**Afinitor** **Current:** Afinitor (everolimus) is available as 2.5 mg, 5 mg and 10 mg tablets for adult patients. The recommended dose is 10 mg everolimus once daily in the Oncology setting. 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. Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of Afinitor 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 (of the EU-SmPC [SmPC]) provides dose adjustment recommendations. Everolimus should be administered orally once daily at the same time every day, consistently either with or without food. Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. **Votubia** **Current:** Votubia (everolimus) is available as 2.5 mg, 5 mg, and 10 mg tablets for adult and pediatric patients with TSC-SEGA and for adult patients with TSC-AML. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. The recommended dose of Votubia is 10 mg once daily for TSC-AML. Management of severe or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of Votubia therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered. Careful titration may be required to obtain the optimal therapeutic effect for TSC-SEGA. The recommended starting dose of Votubia is based on body surface area (BSA). The recommended starting dose for the treatment of patients with SEGA is 4.5 mg/m^2. A starting dose of 7 mg/m^2 is recommended in patients age from 1 year to younger than 3 years of age. Different strengths of dispersible tablets can be combined to attain the desired dose.

	Long-term monitoring with dose adjustments should be evaluated approximately 3 months after start of Votubia therapy, while taking into consideration changes in SEGA volume, tolerability, and corresponding trough concentrations. Therapeutic drug monitoring (TDM) to maintain Cmin within the target concentration range of 5 ng/mL to 15 ng/mL, as described above. Furthermore, for TSC-Seizures, at a starting daily dose of: 6 mg/m^2/day in patients who are younger than 6 years, and 5 mg/m^2/day in patients 6 years and older: both without concomitant administration of CYP3A4 / P-glycoprotein (PgP) inducer. or 9 mg/m^2/day in patients who are younger than 6 years, and 8 mg/m^2/day in patients 6 years and older: both with concomitant administration of CYP3A4 / PgP inducer. Individualized dosing should be titrated by increments of 1 to 4 mg/day to attain target trough concentrations.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Afinitor** **Current:** White to slightly yellowish elongated tablet with a beveled-edge and no score. A tablet will contain 2.5 mg, 5 mg, or 10 mg of everolimus. 2.5-mg oral tablets 5-mg oral tablets 10-mg oral tablets **Votubia** **Current:** White to slightly yellowish elongated tablet with a beveled-edge and no score: a tablet will contain 2.5 mg, 5 mg, and 10 mg of everolimus. White to slightly yellowish round flat tablet with a beveled-edge and no score: a dispersible tablet will contain 2 mg, 3 mg, or 5 mg of everolimus as follows: 2.5-mg oral tablets 5-mg oral tablets 10-mg oral tablets 2-mg dispersible tablets 3-mg dispersible tablets 5-mg dispersible tablets
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

2.1.1 Indication: Renal cell carcinoma

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

Incidence:

Renal cell (renal parenchyma) cancer accounts for 87% to 100% of kidney cancers worldwide (Mathew et al 2002) and about 85% of kidney cancers diagnosed in the US from 1992 through 2002 (Lipworth et al 2009, Protzel et al 2012). In EU, there were approximately 84000 cases of RCC and 35000 deaths due to kidney cancer in 2012 (Ferlay et al 2013). In the US, estimated numbers of annual new cases and deaths of RCC are approximately 63000 and 14000, respectively (Siegel et al 2016).

RCC occurs rarely in children. The incidence of this tumor in childhood is estimated to be from 0.1% to 0.3% of all neoplasms and from 1.8% to 6.3% of all malignant renal tumors (Indolfi et al 2003).

The table below (Lipworth et al 2009) shows incidence rates for RCC in the US by race and sex according to Surveillance, Epidemiology, and End Results (SEER), Program of the National Cancer Institute.

Table 2-1 Incidence rates for renal parenchyma cancer by racial/ethnic group and sex according to US SEER data: 2000 to 2005

Racial/ ethnic group	Males (n)	Rate*	Females (n)	Rate*
White	26195	16.31	15345	8.03
Black	3115	19.24	1884	8.87
Asian	1258	7.80	731	3.67
American Indian	225	12.58	159	7.67
non-Hispanic white	22947	16.43	13232	7.96
Hispanic white	3248	15.81	2113	8.65

*Per 100000 person-years, age adjusted using 2000 US standard

Source: Mathew et al 2002, Lipworth et al 2009, Protzel et al 2012, Ferlay et al 2013, Indolfi et al 2003, SEER, Afinitor / Votubia EU-RMP V13.0 / V13.0- Table 2-1

Prevalence:

For the 28 countries of the EU, data derived from GLOBOCAN (The International Agency for Research on Cancer) shows a 5-year partial prevalence of RCC of 4.93 per 10000 EU population, with about 211479 people living with the disease as of 01-Jan-2012 (Estimated Cancer Incidence Mortality and Prevalence 2012 in Europe: The World Health Organization, GLOBOCAN 2012a).

In 2012, data from Northern European Association of Cancer Registries (NORDCAN) shows a 5-year partial prevalence of 3.6 per 10000 population, 4.3 per 10000, 5.0 per 10000, 4.3 per 10000, and 6.6 per 10000 for Denmark, Finland, Iceland, Norway, and Sweden, respectively (NORDCAN 2012).

Prevalence calculations using GLOBOCAN and NORDCAN data were based on the estimate that RCC represents 85% of all kidney cancers diagnosed (Lipworth et al 2009). SEER data estimates that in 2010 there were approximately 246400 people living with RCC in the US, with a projection to 2020 of about 408800 people living with RCC (Mariotto 2014).

Demographics of the population in the RCC authorized indication – age, sex, racial and/or ethnic origin and risk factors for the disease:

Renal cell carcinoma occurs about twice as often in men as in women. Average age at diagnosis is early sixties in the US (Lipworth et al 2009; Mathew et al 2002).

Rates of RCC vary internationally by about 15-fold, suggesting a strong role for exogenous risk factors (Graves et al 2013). Incidence is generally highest in parts of Western Europe, Scandinavia, and Australia / New Zealand. The lowest rates are reported in parts of Southern Europe, Asia, and Africa (Pascual and Borque 2008, Graves et al 2013).

Geographic distribution by incidence zones (Pascual and Borque 2008, Graves et al 2013)

- High: Denmark, Australia / New Zealand, Norway, Scotland
- Moderate: US, Australia, Belgium, France, Holland
- Low: Spain, Ireland, Italy, Japan, Venezuela, India, China, Africa, Caribbean

In the US, increase in incidence have been more rapid among women than men and among blacks (Lipworth et al 2009).

The main existing treatment options:

Inlyta® (axitinib), as a kinase inhibitor, has been shown to inhibit receptor tyrosine kinases including VEGFR-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models. Axitinib inhibited tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

Inlyta is indicated for the treatment of RCC after failure of one prior systemic therapy, i.e. 2nd line therapy (Anon 2014).

Everolimus is indicated in this patient population (Section 2.1.1).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Renal cell carcinoma is the sixth leading cause of cancer death and is responsible for an estimated 95000 deaths worldwide yearly. Prognosis for RCC appears to have improved. In the US, 5–year survival rates from kidney cancer in the period 1992-1999 (63%) increased compared with 1974 to 1976 (52%) and 1983-1985 (56%) (Drucker 2005). A recent SEER

report shows 5-year relative survival with RCC increased from 63.7% in 1988 to 73.9% in 2002 (Cho et al 2011).

In Sweden, the 5-year survival rate was between 30% to 60% (Lindblad 2004). However, other authors found that for localized renal cell cancer cases, the 5-year relative survival rate is approximately 90% regardless of race or sex (Lipworth et al 2009).

By sex, mortality from kidney cancer in EU in 2006 is reported as 0.49 per 10000 in men and 0.18 per 10000 in women (Bosetti et al 2011).

Important co-morbidities:

The following co-morbidities were found in a study of 1023 patients who underwent radical nephrectomy or nephron-sparing surgery due to their RCC in Germany from 1993 to 2003 (Berdjis et al 2006).

Table 2-2 Key co-morbidity findings

Co-morbidity findings	Age (N=1023)	
	<75 y (%)	≥ 75 y (%)
Cardiac disease		
Coronary artery disease	10.8	37.5
Arrhythmia	4.5	13.3
Myocardial infarction (MI)	4.0	5.3
Vascular disease		
Hypertension	35.4	48.2
Cerebrovascular disease	3.1	6.3
Peripheral vascular disease	1.7	4.5
Respiratory disease		
Chronic obstructive pulmonary disease	3.9	7.1
Metabolic disease		
Diabetes mellitus	12.4	25.8
Renal insufficiency	2.8	6.2
Moderate or severe liver disease	1.7	0.9
Other diseases		
Secondary cancer	7.9	9.8

Source: Berdjis et al 2006

2.1.2 Indication: Advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin (NET)

Neuroendocrine tumours of pancreatic origin

Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors of pancreatic origin in adults with progressive disease

Neuroendocrine tumours of gastrointestinal or lung origin

Afinitor 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

Incidence:

Reports on the epidemiology of NET are not homogenous in the type of tumors included, classification and terminology, with the new WHO classification yet to gain a more worldwide acceptance. Inconsistency of nomenclature of NET is the major limitation in elucidating the epidemiology of pancreatic, gastrointestinal and lung NETs. In most studies, epidemiologic measures are combined for pancreatic NET (P-NET) and gastrointestinal (GI) NET (GI-NET) into gastroenteropancreatic NETs (GEP-NET).

The incidence of GEP-NETs have shown a remarkable increase over the past three decades. The United States Surveillance Epidemiology and End Results (SEER) database and several other European databases currently estimate the GEP-NET incidence at between 2.5 and 6.2 cases / 100000 population (Fraenkel et al 2012).

The project Surveillance of Rare Cancers in Europe (RARECARE) provides the following estimates (Gatta et al 2011):

• Well-differentiated functioning endocrine carcinoma of pancreas and digestive tract tumors (functioning GEPNET): crude annual incidence, 0.02 per 100000 (SE, ±0.00) with 1070 new cases expected per year in the EU containing the following 27 Member States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and UK [defined as EU27];

• Well-differentiated non-functioning endocrine carcinoma of pancreas and digestive tract tumors (non-functioning GEPNET): 1.26 per 100000 (SE, ±0.02) with 63691 new cases expected per year. Of note, additional information by RARECARE indicates the incidence of NET of GI only (islet cell carcinoma, i.e. PNET, cases excluded) of 1.22 per 100000 (RARECARE 2015); and Well-differentiated endocrine carcinoma of lung (NET of lung origin): crude annual incidence, 0.63 per 100,000 (SE, ±0.01) with 3148 new cases expected per year.

Prevalence:

RARECARE provides the following prevalence estimates for the relevant indications (Gatta et al 2011):

• Well-differentiated functioning endocrine carcinoma of the pancreas and digestive tract (functioning GEP-NET): complete prevalence (National Cancer Institute 2010a): 0.21 per 100000 (SE, ±0.02) with 1070 cases expected in the EU27;

• Well-differentiated non-functioning endocrine carcinoma of the pancreas and digestive tract (non-functioning GEPNET): complete prevalence: 12.8 per 100000 (SE, ±0.2) with 63691 cases expected in the EU27; and

• Well-differentiated endocrine carcinoma of the lung (NET of lung origin): complete prevalence: 6.96 per 100000 (SE, ±0.18) with 34627 prevalent cases expected in the EU27.

A population-based study using SEER showed the estimated 29-year limited-duration prevalence (National Cancer Institute 2010b) of all NET in the US of 103312 cases (3.5 per 10000 population) on 01-Jan-2004 (Yao et al 2008).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin [NET]: Advanced NETs can appear at all ages, but are more common in older adults, and a male predominance has been reported for some types of NET (e.g. small intestinal and pancreatic). There are known ethnic differences in the occurrence of advanced NET, with substantial data supporting a higher incidence of these tumors in African Americans (Modlin et al 2003, Hauso et al 2008).

Advanced non-functional NET of GI or lung origin: A study of 10324 cases of GI NET included in the National Cancer Registry for England from 1971 to 2006 reported that the incidence of GI NET increases with age for all sites, with the exception of the appendix. Median age of diagnosis of appendiceal NET was 44.1 years in males and 41.3 years in females; in gastric NET, 68.7 years and 68.7 years, respectively; in small intestinal NET 67.6 years and 68.9 years, respectively; in colon NET, 64.7 years and 64.1 years, respectively; and in rectal NET, 62.8 years and 59.9 years, respectively. For GI NETs, 52% occur in females; appendiceal tumors were more common in females, while small intestinal tumors were more frequent in males (Ellis et al 2010).

Based on literature review, Ferolla et al (2007) reports the mean age of diagnosis of NET of lung origin as 54.1 years ±15.2 (range, 18 to 73 years). No sex prevalence has been reported. However, a female prevalence was seen in patients aged less than 50 years in a large series of 2931 patients.

The main existing treatment options:

At present, surgery is the only curative treatment for NETs.

For advanced NETs, therapeutic options focus on controlling the hormonal syndrome and inhibiting tumor growth. Somatostatin analogs (SSAs) are typically used to control hormonal syndromes, but have also shown to be effective in controlling tumor growth in GEP -NETs. Other options to control tumor growth include interferon (IFN), chemotherapy, surgical resection, or embolization of hepatic metastases and radiation therapy as palliative care. Peptide receptor radiotherapy (radiolabeled therapy) represents an additional option available in a limited number of medical centers. Sunitinib is also approved for the treatment of progressive well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally-advanced or metastatic disease.

Available biologic agents have limited activity against these tumors: (a) somatostatin analogs (SSAs) can reliably control hormone-mediated symptoms and recent evidence indicates that they may also exert an antiproliferative effect in GEP-NET only; and (b) IFN (not approved worldwide for this indication) as retrospective data suggest some evidence of antiproliferative

activity; however, there are limited randomized controlled studies demonstrating an improved outcome compared with patients receiving SSAs or chemotherapy. In addition, the effects of IFN are often reduced as a result of adverse events (AEs) that limit continuous treatment.

Advanced NETs are resistant to most cytotoxic therapies as: (a) no treatment is currently approved globally for tumor control in patients with gastrointestinal or lung NET. Although used, the role of chemotherapy is limited and continues to be debated; in general, it is reserved for high-grade malignancies, which represent only a small minority of this group. Criteria used to determine outcome measures in many earlier trials are considered unacceptable today, while significant toxicities are present for those regimens that demonstrated improved response rates; and (b) streptozocin is approved in the US, Canada, France, and Israel, primarily for pancreatic NET. Streptozocin–based regimens form the backbone for the treatment of pNET. Response rates of approximately 40% have been reported in combination with 5-fluorouracil (FU) or doxorubicin; however, benefits in terms of progression-free survival (PFS) or overall survival (OS) advantages have not been observed.

Response rate data are difficult to interpret as the definition of response included clinical response, CgA response, and radiological response (WHO criteria) when the initial trials were performed.

Everolimus is indicated in patients with advanced pancreatic NET [pNET] (Section 2.1.2).

Advanced non-functional NET of GI or lung origin:

Lanreotide is approved for the treatment of patients with unresectable, well - or moderatelydifferentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEPNETs).

However, the clinical study population (Caplin et al 2014) for the approval had a good prognosis by including patients with non-progressing disease with Ki-67 ≤ 10% who mostly had received no prior therapy.

Therefore, no approved therapeutic options exist for patients with advanced progressing non-functional GI NET or NET of lung origin.

Natural history of the indicated condition in the population, including mortality and morbidity:

The 5-year survival probability in patients with advanced NET histologic grade 1 and grade 2 are 82%, 68%, and 35% for localized, regional, and distant disease, respectively; with a median survival of 223, 111, and 33 months, respectively.

The 5-year survival probability in patients with histologic grade 3 and grade 4 are 38%, 21%, and 4% for localized, regional, and distant disease, respectively; with a median survival of 34, 14, and 5 months, respectively (Yao et al 2008).

RARECARE provides the following estimates (Gatta et al 2011):

- Well-differentiated functioning endocrine carcinoma of pancreas and digestive tract: observed 5-year survival, 45.5%; relative 5-year survival (the ratio of observed survival to the expected survival in the general population of the same age and sex), 50.4%

- Well-differentiated non-functioning endocrine carcinoma of pancreas and digestive tract: observed 5-year survival, 55.6%; relative 5-year survival (the ratio of observed survival to the expected survival in the general population of the same age and sex), 64.3%
- Well-differentiated endocrine carcinoma of lung: observed 5-year survival, 27.6%; relative 5-year survival (the ratio of observed survival to the expected survival in the general population of the same age and sex), 32.2%

Important co-morbidities:

Neuroendocrine tumors (NET) including pNET constitute a heterogeneous group of neoplasms that may present with a variety of functional or nonfunctional syndromes. The table below presents data on functional clinical syndromes according to Kaltsas et al (2004) and, in two instances, according to Bernheim et al (2007) and Soga and Yakuwa (1998), according to tumor type:

Table 2-3 Key co-morbidity findings

Co-morbidity findings	Syndromes
Neuroendocrine tumor (NET) / Carcinoid	Carcinoid syndrome, 20% to 30%: flushing, 90% diarrhea, 70% abdominal pain, 40% valvular heart disease, 40% to 45% telangiectasia, 25% wheezing, 15% pellagra, 5%
Insulinoma	Neuroglycopenia, 100%
Gastrinoma	Zollinger-Ellison syndrome, 100%: peptic ulcer, 90% diarrhea, 50% to 60%
Glucagonoma	Glucagonoma (diabetico-dermatogenic) syndrome, 60%: weight loss, 70% to 80% rash (necrotic migratory erythema) 65% to 80% diabetes, 75% cheilosis or stomatitis, 30% to 40% psychiatric disorders, ≤ 30% thromboembolism, ≤ 30%
VIPoma	Verner-Morrison (WDHA-watery diarrhea hypokalemia achlorhydria) syndrome, 100%: diarrhea, 100% (intermittent, 53%; continuous, 47%) achlorhydria or hypochlorhydria, 70% carbohydrate intolerance, 50% facial flushing, 20%
Somatostatinoma	Somatostatin syndrome, 11%: hyperglycemia, 95% cholelithiasis, 26% diarrhea, 60%

	steatorrhea, 47% hypochlorhydria, 26%

Source: Kaltsas et al (2004), Bernheim et al (2007), Soga and Yakuwa (1998)

2.1.3 Indication: Advanced breast cancer in postmenopausal women (BREAST)

Afinitor 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.

Incidence:

World: The world age-standardized incidence rate in 2012 was estimated as 43.1 per 100000 women, although its frequency varies nearly 4-fold across the world regions (GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d)

EU: The EU age-standardized incidence rate in 2012 was estimated as 80.3 per 100000 women. Incidence rates in the EU27 and Croatia [defined as EU28] are presented in Table 2-5 (GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d). In European countries, based on EUROCARE data (1996 to 1998 that includes 26 cancer registries from 12 countries), the percentage of breast cancer is 8% and 6%, respectively (Allemani et al 2013).

US: Based on SEER cases diagnosed in 2007 to 2011 (SEER 2015a), the age-adjusted incidence rate was 124.6 per 100000 women per year.

Incidence rates by stage III or IV breast cancer per 100000 person years in women 50 years of age or older for the period of 2000 to 2012 were 36.5 and 16.9, respectively (SEER 2015b).

By breast cancer subtype (hormone receptor (HR) and HER2 status), the most frequent is usually the HR-positive and HER2- negative (luminal type). In the US, based on data from the SEER registry, among patients with stage III, the frequency of HR+/HER2- breast cancer was 62.6% and among those with a stage IV diagnosis, 61.2% (Howlader et al 2014). In Poland, 69% of patients with invasive breast cancer had a luminal A subtype and 6% luminal B subtype (Yang et al 2007).

Incidence rates by race per 100000 women were estimated as follows: all races, 124.6; white, 128.0; black, 122.8; Asian/Pacific Islander, 93.6; American Indian/Alaska Native, 79.3; Hispanic, 91.3; non-Hispanic, 129.7.

Prevalence:

World: In 2012, the estimated 5-year prevalence was 240 per 100000 women (Table 2-4 and Bray et al 2013).

EU: In 2012, the estimated 5-year prevalence was 654 per 100000 women ranging from 354 per 100000 in Romania to 899 in Belgium (Table 2-5 and Bray et al 2013).

US: In 2011, there were an estimated 2899726 women living with breast cancer (SEER 2015a).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

From 2004 to 2008, the median age at diagnosis for breast cancer was 61 years of age. Approximately 0% cases were diagnosed under age 20; 1.9% between 20 and 34; 10.2% between 35 and 44; 22.6% between 45 and 54; 24.4% between 55 and 64; 19.7% between 65 and 74; 15.5% between 75 and 84; and 5.6% ≥ 85 years of age (SEER 2011, GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d, Bray et al 2013).

Table 2-4 Incidence, prevalence, and mortality of female breast cancer in the world (standardized to the world population)

Regions	Incidence (per 100000 person-year)	5-Year prevalence (per 100000 population)	Mortality (per 100000 person-year)
Table	42-53.1	239.9	12.9
Africa	36.2	134.7	17.3
Latin America and Caribbean	47.2	243.8	13.0
North America	91.6	744.5	14.8
Asia	29.1	146.3	10.2
Europe	69.9	553.8	16.1
Oceania	79.2	530.0	15.6
Micronesia / Polynesia	59.7	161.9	13.1

GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d, Bray et al 2013

Table 2-5 Incidence, prevalence, and mortality of female breast cancer in the EU (standardized to the world population)

Country	Incidence (per 100000 person-year)	5-Year prevalence (per 100000 population)	Mortality (per 100000 person-year)
Austria	68.0	551.4	14.4
Belgium	111.9	899.4	20.3
Bulgaria	58.5	440.2	17.2
Croatia	60.9	549.4	16.7
Cyprus	78.4	553.0	14.9
Czech Republic	70.3	547.2	12.8
Denmark	105.0	887.4	18.8
Estonia	51.6	388.3	15.7
Finland	89.4	809.2	13.6
France	89.7	771.0	16.4
Germany	91.6	765.7	15.5
Greece	43.9	400.7	14.1
Hungary	54.5	415.5	16.2

Ireland	92.3	625.9	19.1
Italy	91.3	775.6	15.8
Latvia	52.1	401.4	17.6
Lithuania	48.7	358.6	16.3
Luxembourg	89.1	727.4	13.1
Malta	85.9	678.4	18.1
Poland	51.9	397.0	13.8
Portugal	67.6	512.2	13.1
Romania	50.0	353.7	15.2
Slovakia	57.5	388.8	13.1
Slovenia	66.5	540.1	15.6
Spain	67.3	516.2	11.8
Sweden	80.4	687.4	13.4
The Netherlands	99.0	821.4	18.0
United Kingdom	95.0	755.1	17.1

GLOBOCAN 2012a, GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d, Bray et al 2013

The main existing treatment options:

Non-steroidal aromatase inhibitors (NSAIs; letrozole and anastrozole) are generally the treatment of choice for postmenopausal women with hormone-receptor-positive breast cancer. Unfortunately, not all patients respond to first-line endocrine therapy (as a result of de novo resistance) and patients who initially respond to treatment will eventually relapse (due to acquired resistance). Following recurrence or progression on letrozole or anastrozole, limited endocrine treatment options exist. The most commonly followed treatment sequence includes exemestane and fulvestrant. These two options demonstrated similar limited efficacy in the Phase-III EFECT study, with a median PFS of only 3.7 months. Other endocrine options, e.g. tamoxifen, in this setting have not been adequately evaluated in randomized clinical trials. The benefit from second and subsequent lines of endocrine is usually limited and of shorter duration than that of first-line therapy. Resistance to endocrine therapy, either de novo or acquired, is therefore a major limitation in the current treatment of patients with hormone-receptor-positive advanced breast cancer.

The addition of everolimus to endocrine therapy results in an improved clinical outcome and has since become a standard treatment option for postmenopausal women with ER+/HER2- advanced breast cancer, in combination with an aromatase inhibitor (AI), after prior endocrine therapy. Palbociclib, an oral inhibitor of cyclin-dependent kinases (CDKs) 4/6, was approved by FDA for combination use with letrozole, for the treatment of postmenopausal women with ER+/HER2- advanced breast cancer as an initial endocrine-based therapy.

Everolimus is indicated in this patient population (Section 2.1.3).

Table 2-6 Previous chemotherapy and prior trastuzumab or taxane use in breast cancer patients (Full Analysis Set)

	Everolimus + exemestane N=485 n (%)	Placebo + exemestane N=239 n (%)
CRAD001Y2301 (DCO, 11-Feb-2011)		
Previous chemotherapy		
Both adjuvant/neoadjuvant and metastatic	58 (12.0)	38 (15.9)
Metastatic only	67 (13.8)	23 (9.6)
Adjuvant/neoadjuvant only	211 (43.5)	95 (39.7)
Prior use of NSAI		
Both adjuvant/neoadjuvant and metastatic	20 (4.1)	12 (5.0)
Metastatic only	323 (66.6)	170 (71.1)
Adjuvant/neoadjuvant only	137 (28.2)	55 (23.0)
Prior hormonal therapy other than NSAI	281 (57.9)	146 (61.1)

Source: Afinitor / Votubia EU-RMP V12.1 / V12.1-Table 2-4

	Everolimus + trastuzumab + vinorelbine N=280 n (%)	Placebo + trastuzumab + vinorelbine N=282 n (%)
CRAD001W2301 (DCO, 15-Mar-2013)		
Previous chemotherapy	280 (100)	282 (100)
Both adjuvant / metastatic	136 (48.6)	137 (48.6)
Metastatic only	77 (27.5)	87 (30.9)
Adjuvant / neoadjuvant only	67 (23.9)	58 (20.6)
Prior use of trastuzumab	279 (99.6)	282 (100)
Both adjuvant / metastatic	51 (18.2)	55 (19.5)
Metastatic only	150 (53.6)	163 (57.8)
Adjuvant / neoadjuvant only	78 (27.9)	64 (22.7)
Prior use of taxane	279 (99.6)	282 (100)
Both adjuvant / metastatic	54 (19.3)	45 (16.0)
Metastatic only	127 (45.4)	145 (51.4)
Adjuvant/neoadjuvant only	98 (35.0)	92 (32.6)

Source: André et al 2014

Natural history of the indicated condition in the population, including mortality and morbidity:

World: The world age-standardized mortality rate in 2012 was estimated as 12.9 per 100000 women, ranging from 6.1 per 100000 in Eastern Asia to 20.1 per 100000 in Western Africa (GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d).

EU: The EU age-standardized mortality rate in 2012 was estimated as 15.5 per 100000 women (GLOBOCAN 2012b, GLOBOCAN 2012c, GLOBOCAN 2012d). Mortality rates by EU28 countries are presented in Table 2-4.

US: From 2007 to 2011, the median age at death for cancer of the breast was 68 years. Approximately 0% died under age 20; 0.9% between 20 and 34; 5.2% between 35 and 44; 14.5% between 45 and 54; 21.7% between 55 and 64; 20.6% between 65 and 74; 21.0% between 75 and 84; and 16.2%, ≥ 85 years of age. Based on patients who died in 2007 to 2011 in the US, the age-adjusted death rate was 22.2 per 100000 women per year. Death rates by race per 100000 women were estimated as follows: all races, 22.2; white, 21.7; black, 30.6; Asian/Pacific Islander, 11.3; American Indian/Alaska Native, 15.2; Hispanic, 14.5; non-Hispanic, 22.9. The overall 5-year relative survival for 2004-2010 from 18 SEER geographic areas was 89.2%. Five-year relative survival by stage at diagnosis was: for localized disease (confined to primary site) – 98.5%, for regional disease (spread to regional lymph nodes) – 84.6%, for distant disease (metastasized cancer) – 25.0% (SEER 2015a).

Important co-morbidities:

Patnaik et al (2011) used Surveillance, Epidemiology, End-Results, and Medicare data to describe comorbidity in breast cancer among 64034 women aged equal or greater than 66 years from 1992 to 2000. In decreasing prevalence, a total of thirteen co-morbid conditions are summarized in the table below. None of these thirteen co-morbid conditions were identified in 37306 (58%) of the study population.

Table 2-7 Key co-morbidity findings for Advanced breast cancer in postmenopausal women [BREAST]

	Prevalence (%)	Mortality (adjusted hazard ratio (HR) (95% CI))
No co-morbid condition	58.3	1.0 (referent)
Co-morbid conditions:		
Previous cancer	16.3	1.27 (1.23, 1.30)
Diabetes	13.0	1.41 (1.36, 1.45)
Chronic obstructive pulmonary disease (COPD)	8.8	1.52 (1.47, 1.58)
Congestive heart failure	6.7	1.70 (1.64, 1.76)
Cerebrovascular disease	4.3	1.35 (1.28, 1.42)
Peripheral vascular disease	2.6	1.36 (1.28, 1.44)
Rheumatoid arthritis	2.0	1.27 (1.18, 1.37)
MI	1.7	1.11 (1.03, 1.19)
Dementia	1.4	1.96 (1.82, 2.10)
Stomach ulcer	1.1	1.12 (1.02, 1.23)
Chronic renal failure	0.9	2.20 (2.02, 2.41)
Paralysis	0.6	1.23 (1.09, 1.38)
Liver disease	0.3	2.32 (1.97, 2.73)

The prevalence of number of comorbidities at diagnosis and its incidence after diagnosis in women with stage III to IV breast cancer in the US is presented in table below (Danese et al 2012).

Prevalence and incidence of comorbid conditions in women diagnosed of Stages III and IV breast cancer in the US:

Co-morbidity	Prevalence (%)		3-month incidence rate (per 1000 patient-years)	
	Stage III	Stage IV	Stage III	Stage IV
		Cardiac / vascular		
Hypertension	51	42.46	611.48	642.25
Coronary artery disease	18.97	14.01	112.61	152.88
Congestive heart failure	10.16	7.08	122.48	292.86
Cerebrovascular disease	12.53	11.31	94.29	109.35
Atrial fibrillation	8.07	7.9	130	172.74
Arrhythmia	6.76	5.14	114.22	89.43
MI	4.78	3.11	77.43	70.92
Peripheral vascular disease	3.26	2.48	32.99	45.68
Thromboembolism	2.27	2.45	42.52	208.33
Arterial thrombosis	0.29	0.35	4.72	13.3
Cardiac arrest	0.2	0.13	5.49	16.28
		Gastrointestinal / hepatic		
Cholecystitis	1.16	1.49	15.2	39.99
Gastric ulcers	0.55	0.65	11.9	24.54
Liver disease	0.33	0.79	7.91	13.86
		Metabolic		
Diabetes	16.89	15.39	74.94	132.74
Hyperglycemia	0.05	0	0	3.64
		Musculoskeletal / rheumatic		
Osteoarthritis	13.37	9.2	93.23	120.5
Rheumatologic disease	2.09	1.57	8.69	15.75
		Neurological / psychiatric		
Alzheimer's disease and dementia	6.05	3.49	79.77	84.64
Depression	4.97	4.92	70.41	171.86
Hemiplegia	1.53	0.95	20.13	22.04
		Pulmonary		
Chronic obstructive pulmonary disease	10.41	9.52	133.86	289.19
		Renal		
Renal disease	1.52	1.35	19.57	40.32
Nephrotic syndrome	0.06	0.22	0	0

Source : Patnaik et al (2011), Danese et al (2012)

2.2 Indications in TSC setting

2.2.1 Indication : Subependymal giant cell astrocytomas associated with TSC (TSC-SEGA)

Votubia is indicated for the treatment of adult and paediatric patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated

Incidence:

Subependymal giant cell astrocytomas have been described as very rare tumors; however, no published data on the absolute incidence have been found. Subependymal giant cell astrocytoma is diagnosed in 5% to 20% of patients with TSC.

Between 1954 and 1984, 282 children with astrocytoma were reported to the population based Manchester Children's Tumour Registry, including four children with TSC. The calculated incidence of astrocytoma associated with TSC in this population was 0.13 per million person-years (Kibirige et al 1989).

Prevalence:

No published data on the absolute prevalence of SEGA in the general population have been found.

The prevalence of SEGA in TSC reported from population-based studies varied from 6% to 20% (Shepherd et al 1991c, Adriaensen et al 2009) or higher, depending on the diagnosis method. O'Callaghan et al (2008) evaluated the prevalence of SEGA among 179 TSC patients identified in Wessex, England. The proportion of people with TSC who had a history of a symptomatic SEGA was 5.6%. In the subset of patients without such a history, who underwent cranial magnetic resonance imaging (MRI) (n=41), 17% had evidence of the lesion with diameter of >1 cm and 59% had at least one nodule that was enhanced after administration of intravenous gadolinium. A meta-analysis of the reported prevalence of SEGA in TSC showed that studies using radiological evidence to diagnose SEGA gave a higher pooled estimate of the prevalence (16%; 95% confidence interval (CI): 12, 21) than studies using mainly histopathological evidence to diagnose SEGA (9%; 95% CI: 7, 12) (Adriaensen et al 2009).

The following prevalence of TSC has been reported from population-based studies conducted in the EU and US:

- 7.75 per 100000 in Western Sweden (Ahlsen et al 1994) 4 per 100000 in Northern Ireland (Devlin et al 2006)
- 4.9 per 100000 in Wessex region of England (O'Callaghan et al 2008)
- 6.9 per 100000 in Olmsted County, Minnesota, US (Shepherd et al 1991a)
- 1 per 95136 in Taiwan (Hong et al 2009)

Assuming the average TSC prevalence of approximately 6 per 100000 population and applying to it the range of the proportions of SEGA among TSC of 6% to 20%, the prevalence of SEGA associated with TSC can be estimated in a range from 0.36 to 1.2 per 100000 population.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The natural history of SEGA is not fully elucidated. According to Torres et al (2001), the growth of SEGA peaks at puberty and stops by the end of the third decade of life. In most published series of SEGA patients, the mean age at clinical diagnosis was less than 18 years. Only one study by Webb et al (1996) described 9 symptomatic patients with a mean age of 24 years (range, 13 to 39 years) (Adriaensen et al 2009).

The main existing treatment options:

In most countries, the standard of care for these TSC indications is surgery or embolization with no effective alternative having been identified to date.

The only treatment option for SEGA with TSC, a rare brain tumor, is surgical resection. Surgical techniques are improving, with few alternatives demonstrating proven benefit. More recent advances include the fully automated robotic Gamma Knife system, which administers gamma radiation to the brain without surgical incision to the skull. New treatment options, such as pharmaco- therapeutic interventions, should also include pediatric dosage forms.

Everolimus is indicated in this patient population (Section 2.2.1)

Natural history of the indicated condition in the population, including mortality and morbidity:

Subependymal giant cell astrocytomas are potentially lethal and have been shown to be responsible for 25% of the mortality due to TSC (Shepherd et al 1991b). Mean life expectancy for TSC is 50 years, with the maximum age of approximately 70 years (Coppus 2013).

Important co-morbidities:

Subependymal giant cell astrocytomas are histologically benign but locally invasive. Because of their location and growth potential, SEGAs can cause increased intracranial pressure (visual disturbances, headaches), obstructive hydrocephalus, and focal neurologic deficits. The recently published series of relatively large number of patients with SEGA described the prevalence of clinical and radiological symptoms as follows:

- Hydrocephalus: In the series of 43 patients with radiological diagnosis of SEGA evaluated between August 1996 and February 2007 in a nationwide tertiary referral center for TSC in Utrecht, Netherlands, 6 (14%) patients had hydrocephalus (Adriaensen et al 2009). Among 15 patients requiring surgical intervention because of SEGA in the Hospital Nacional de Pediatria in Buenos Aires, Argentina between January 1998 and December 2000, 12 (80%) patients had hydrocephalus. Among 11 patients who underwent resection of pathologically confirmed SEGA at the Massachusetts General Hospital in Boston, MA between December 2001 and November 2003, 6 (56%) patients had hydrocephalus and 3 (27%) had visual field deficit (Goh et al 2004).

- Intracranial pressure: Eleven (73%) patients had increased intracranial pressure, and 3 (20%) had focal motor defects. In addition, the patients presented with other clinical findings typical of TSC; all 15 had skin lesions, 14 (93%) has seizures, 3 (20%) had cardiac tumors, and 1 (6.7%) had a renal tumor (Cuccia et al 2003).

2.2.2 Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery.

The evidence is based on analysis of change in sum of angiomyolipoma volume.

Incidence:

No published population based data have been identified.

A couple of papers reported renal angiomyolipoma to have an incidence of about 0.3% to 3% and indicated that 20% of these tumors are associated with TSC (Nasir and Ahmad 2010, Mittal et al 2011). Thus, the incidence of AML associated with TSC can be estimated as 0.06% to 0.6%.

Prevalence:

Renal angiomyolipoma is one of major features among diagnostic criteria for TSC. The prevalence of angiomyolipomas in TSC patients estimated from population based studies ranges from 34% to 69% (Webb et al 1994, O'Callaghan et al 2004).

Based on the statement by Bissler and Kingswood (2004) in this publication, "there are over 10 million people world-wide with renal angiomyolipoma and approximately one tenth of these also have tuberous sclerosis", it can be estimated that the number of TSC patients who have angiomyolipoma associated with TSC exceeds 1000000 worldwide.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Multiple, bilateral renal angiomyolipomas are found in about 70% to 90% of adult patients with TSC. Angiomyolipomas are more often symptomatic in women. In one report of a retrospective record review of 167 patients (age range, 1-month-old to 59-year-olds) with TSC, angiomyolipoma was more common in females than males (Rakowski et al 2006). The angiomyolipoma prevalence is lower in children, but up to 16% of TSC patients aged less than 2 years can be affected. As the incidence and size of angiomyolipomas increase with age, angiomyolipoma does become an important cause of morbidity and mortality among adults with TSC (Curatolo et al 2002).

The main existing treatment options:

Renal angiomyolipomas are one of the greatest causes of morbidity and mortality in adult TSC patients, which can be one of the most challenging aspects of the disease to treat. Standard of

care includes nephrectomy or embolization. There are emerging options under development, e.g. radiofrequency ablation. The impetus in these patients is the reduction of kidney tumor burden.

Everolimus is indicated in this patient population (Section 2.2.2).

Natural history of the indicated condition in the population, including mortality and morbidity:

Although renal complications are the leading cause of death in TSC patients (De Waele et al 2014), no published quantitative data on the risk of mortality directly related to angiomyolipoma have been found. Mean life expectancy for TSC is 50 years, with the maximum age of approximately 70 years (Coppus 2013).

Important co-morbidities:

No published population-based study provided data on co-morbidity in patients with TSC who have angiomyolipoma. However, some population-based data have been published on the frequency of symptoms and complications from renal angiomyolipoma.

Cook et al (1996) showed that 13 (9.4%) of 139 TSC patients had a history of symptoms attributable to their renal disease, most commonly frank hematuria from bleeding angiomyolipomas, and three patients (2.2%) had renal carcinoma.

Many patients have neurologic co-morbidities since about 85% of children and adolescents with TSC have central nervous system (CNS) complications, including epilepsy, cognitive impairment, behavioral problems, and autism (Curatolo et al 2002).

Renal angiomyolipoma in female patients with TSC is associated with the development of pulmonary lymphangioleiomyomatosis (LAM): angiomyolipoma is observed in approximately 88% of patients with TSC and LAM; LAM usually predates the onset of pulmonary disease (Ryu et al 2006).

Case reports have been published describing hypertension in patients with TSC who have angiomyolipoma (Green et al 1990); however, no frequency data have been identified.

2.2.3 Refractory Seizures with Tuberous Sclerosis Complex (TSC-Seizures)

Refractory seizures associated with TSC [TSC-Seizures], which is for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC

Incidence:

Evidence from hospital-based studies in TSC patients suggest that seizures occur in approximately 80% to 90% of TSC patients (Thiele 2004), which are often refractory to antiepileptic treatment (Curatolo et al 2008, Moavero et al 2010).

Results from a retrospective chart review of 291 TSC patients revealed more than 12% of adult patients affected by TSC without a prior history of seizure develop epilepsy suggesting that TSC patients remain at risk for epilepsy throughout their lifetime (Chu- Shore et al 2010). A Japanese study, including 166 TSC patients treated at Osaka University Hospital between 2001

to 2011, report that 20% of TSC patients had refractory epilepsy (with at least 2 uncontrolled seizures within a week, despite the administration of more than two different antiepileptic drugs) (Wataya-Kaneda et al 2013). In a population based-study in younger (less than 16 years) TSC patients, newly diagnosed patients with TSC in the UK were evaluated. The median age of participants were 2.7 years and of 125 cases included in the analysis, 77 cases (62%) presented with seizures (Yates et al 2011).

Prevalence:

No published data on the absolute prevalence of refractory seizures in the general population have been found.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

In comparison to TSC patients with epilepsy who are controlled, patients with refractory seizures are younger at diagnosis, have a higher history of infantile spasms (37.3%, refractory seizures group vs. 21.1%, epilepsy controlled group) and / or Lennox-Gastaut Syndrome, lower educational achievement, higher prevalence of psychiatric disorders (i.e. autism), and more TSC2 mutations (Jansen et al 2008, Vignoli et al 2013, Wataya-Kaneda et al 2013).

The main existing treatment options:

Patients with TSC may manage their symptoms of seizures with AEDs or with nonpharmacological epilepsy treatments of ketogenic and low glycemic index diets, vagal nerve stimulation (VNS), or epilepsy surgery (CIOMS 1998, Jobst 2009, Wong 2010). Yet, seizures associated with TSC are poorly controlled by these treatment options: up to 60% of patients with TSC-associated epilepsy fail to demonstrate improvement in seizure frequency with available therapies (Franz et al 2001, Collins et al 2006, Jennesson et al 2013).

More importantly, the underlying challenges with AEDs is they are prescribed based on manifestation of clinical signs and symptoms, and not based on disease etiology of seizures.

Seizures are traditionally categorized into two major groups: generalized onset seizures and partial onset seizures. Currently approved drugs are typically used for either generalized onset seizures or partial onset seizures. In this case, seizure management is attempted while ignoring disease etiology. The aforementioned classification of seizures does not benefit patients with TSC who have multifocal disease that most typically causes mixed seizures resembling both generalized onset and partial onset seizures. Similarly, a strategy of using drugs targeting either partial onset or generalized seizures does not usually succeed.

Patients with TSC express multiple partial onset seizures or generalized onset seizures, or a mixture of both. Seizure manifestations are not mutually exclusive. TSC patients have a unique challenge in controlling their symptoms of mixed seizure-types. Seizures in TSC have an underlying etiology and common pathogenesis due to the mutation and mTOR overactivation.

Vigabatrin (Sabril®) is one of the currently approved AEDs, which is a reasonable choice as stated by the International TSC Consensus Conference (Curatolo et al 2002). Although currently indicated for infantile spasms in infants and toddlers as a monotherapy, vigabatrin has not been studied in an adequately controlled, double-blind clinical study in patients with TSC

(Anon 2015). The precise mechanism of anti-seizure activity is unknown; however, vigabatrin has demonstrated mTOR inhibition properties in the mouse species (Zhang et al 2013). Currently, speculation on the mechanism includes irreversible inhibition of GABA-T, which is the enzyme responsible for metabolism of GABA (Anon 2015). Off-label use of vigabatrin in TSC patients with seizures has been reported (NORD 2016).

Epilepsy surgery has improved over time. The latest advances in stereotactic radiosurgery (SRS), e.g. the Perfexion® system, are summarized below and have been previously discussed in Afinitor / Votubia PSUR 7- Section 18.1. Resection of epileptic foci can, as well, be delivered by robotic devices that assist neurosurgeons with precise navigation via SRS, e.g. ROSA™ Brain. However, it is reported that approximately a third of patients with TSC continue to experience seizures even after surgical intervention (Curatolo et al 2006, Jansen et al 2007, Napolioni et al 2009).

Finally, the ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that is used primarily to treat difficult-to-control (refractory) epilepsy in children. This diet forces the body to burn fat rather than carbohydrate.

Vagus Nerve Stimulation (VNS) is a medical treatment that involves delivery of electrical impulses to the vagus nerve. It is used as an adjunctive treatment for certain types of intractable epilepsy and treatment-resistant depression.

Everolimus is indicated in this patient population (Section 2.2.3).

Natural history of the indicated condition in the population, including mortality and morbidity:

No mortality data in the target population have been found.

Data from studies on all types of epilepsy reveal that patients with epilepsy are on average 2 to 11 times at higher risk of mortality, compared to the general population, mostly because of sudden unexpected death in epilepsy (SUDEP), accidents, suicide, vascular disease, pneumonia, and factors directly related to the underlying causes (e.g. brain tumors, neurodegenerative disease) (Fazel et al 2013, Holst et al 2013, Laxer et al 2014). SUDEP is the most common direct epilepsy-related cause of death, often in relation to a seizure (Tomson et al 2005).

By seizure type, mortality is greatest for patients with refractory seizures (Trinka et al 2013).

Important co-morbidities:

No comorbidity data specifically in refractory seizures associated with TSC were found.

In a chart review study done in the US between 2007 to 2009 including patients with TSC, about 72% of TSC patients had more than 1 psychiatric disorder (Chung et al 2011).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
Single and repeat-dose toxicity	Everolimus showed a low acute toxic potential after oral administration in mice and rats. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats. The low oral acute toxicity indicates that there is a minimal risk of intoxication following accidental or deliberate overdosing. Studies in mice over 13 weeks, in rats up to 26 weeks, in minipigs up to 4 weeks, and in monkeys up to 52 weeks. In general, repeated oral administration of everolimus to mice, rats, monkeys and minipigs was not associated with any specific clinical signs. Reduced body weight gain in all species at higher dose levels, e.g. ≥ 5 mg/kg in mice, ≥ 0.5 mg/kg in rats, ≥ 1.5 mg/kg in minipigs and ≥ 0.5 mg/kg in monkeys, may be partly related to possible effects of everolimus on absorptional functions of the intestine as reported for rapamycin in rats (Yanchar et al 1996). A considerable number of the findings observed in the toxicity studies are due to pharmacological effects of the compound. These include atrophic changes in lymphatic organs such as thymus, spleen, and lymph nodes associated with a decrease in circulating lymphoid as well as total white blood cells. These showed full or at least partial reversibility after a 2- or 4-week recovery period. Effects secondary to immunosuppression were evident at higher dosages in all species. These included a variety of skin alterations (e.g. abrasions, ulceration, inflammation, scabs) in the 4-week monkey study at ≥ 5 mg/kg and in the 13-week mouse study at ≥ 1.5 mg/kg where this effect was considered to be a dose-limiting factor for the mouse carcinogenicity study. Spontaneous heart lesions (myocardial degeneration, also reported as chronic myocarditis) in the rat were exacerbated by treatment with everolimus, generally at doses ≥ 1.5 mg/kg. Although this was not consistently seen in all studies; the pathogenesis of these heart lesions is unknown; similar findings reported for rapamycin; Chan et al (1995); DiJoseph and Sehgal (1996) were attributed to pre-existing parvovirus (Vu et al 1997). Intestinal disorders associated with diarrhea led to poor general health condition and some early sacrifices in minipigs and monkeys. This was evident in the 4-week study in minipigs from an exacerbation of coccidial infestation in the intestine, and in the 52-week study in monkeys from inflammatory changes in the

Key safety findings (from non-clinical studies)	Relevance to human usage
	gastrointestinal (GI) tract, which contributed to the premature termination of the high-dose group at 0.9 mg/kg after 39 weeks. Major target organs in all species were reproductive organs. Histopathological findings consisted mainly of depletion of germ cells and tubular vacuolation in testes, reduced sperm content in epididymides, reduced ovarian follicular development, and uterine atrophy. Effects on the reproductive organs, including decreases in the respective organ weights, were generally evident at dosages of ≥ 0.5 mg/kg with the exception of testicular atrophy in monkeys at 0.3 mg/kg after 52 weeks of treatment. Reversibility of changes in male reproductive organs was demonstrated in a 13-week rat study at 0.5 mg/kg after 13 weeks of recovery, whereas at 5.0 mg/kg full recovery was achieved in only half of the animals. No reversibility was observed in rats; or minipigs after a recovery period of 4 weeks which is, however, too short for this type of lesion. Similar findings in reproductive organs of rats were also observed in a comparative study with rapamycin. Moreover, testicular atrophy has also been reported in mice and monkeys treated with rapamycin (Morris 1992). These findings suggest a relationship to an endocrine imbalance, which was evidenced in rats by a decrease in circulating testosterone levels after everolimus and rapamycin. A similar etiology is suggested for the delay in testes descent observed after the oral administration of everolimus or rapamycin to neonatal/juvenile rats. Other target organs were identified only in single species, sometimes not consistently, and might represent species-specific effects. A slight depletion of cortical bone in the 4-week rat studies at ≥ 5.0 mg/kg; might also be related to the above mentioned hormonal imbalance (Prakasam et al 1999). Administration for 2 years in rats up to 0.9 mg/kg, however, was not associated with adverse bone effects. A decrease in pituitary weight without histopathological correlate was only observed in the rat, but similarly occurred with other immunosuppressive compounds such as rapamycin and tacrolimus and therefore is considered to be a species-specific effect of immunosuppressants. In comparison to controls, the finding of dilated lateral ventricles in the brain of rats treated with everolimus or rapamycin was exacerbated at higher dosages only in the 2-week studies, but not at longer duration or in other species. This species-specific finding suggests an acute effect which is not considered to be of toxicological significance. A target organ identified in rats and to a minor degree in mice, and therefore probably rodent-specific, was the lung. An increased number of alveolar macrophages was detected at ≥ 1.5 mg/kg in the mouse and at ≥ 0.5 mg/kg in the rat. Electron microscopic examinations of rat lungs revealed vacuoles and multilamellar bodies in the macrophages, suggestive of a storage disorder of lipoproteins.

Key safety findings (from non-clinical studies)	Relevance to human usage
	In the rat eyes, swelling/disruption of cortical lens fibers occurred at ≥ 5 mg/kg. This finding was further investigated with a specific study of two different strains and ages of animals. Findings of lenticular anterior suture lines (at ophthalmic examination), and of swelling/disruption of cortical lens fibers (at histopathological evaluation), were present in both strains of rats. Young animals appeared to be more susceptible than old animals, and the CD strain was more susceptible than the HanIbm Wistar strain. In view of the absence of similar findings in other species, even after life-long treatment in the mouse, these effects are regarded as rat-specific. Kidney lesions as reported for immunosuppressive compounds inhibiting calcineurin pathways were not observed with everolimus. Renal tubular degeneration in CD-1 mice after 13 weeks of treatment at ≥ 5 mg/kg was possibly related to the exacerbation of pre-existing interstitial inflammation, possibly as a consequence of immunosuppression and/or an impaired regeneration of renal lesions as reported for rapamycin (Lieberthal et al 2001). There was no indication of kidney toxicity in mice after life-long treatment up to 0.9 mg/kg. In rats, incidence and severity of lipofuscin in renal tubular epithelial cells was more pronounced in treated animals at ≥ 0.3 mg/kg than in controls of the oncogenicity study and occurred already after 26 weeks of treatment at ≥ 0.5 mg/kg. The incidence and severity of lipofuscin in renal tubular epithelial cells points to an increased degradation of membrane phospholipids and an acceleration of a normal, age-related process. Increased incidence of hydronephrosis was observed in male rats at ≥ 0.5 mg/kg in the 26-week study. Increased incidence of hydronephrosis was observed in a small number of male rats at ≥ 0.5 mg/kg in the 6-month study. These were considered reversible and were not seen in rats of the 2-year carcinogenicity study at doses up to 0.9 mg/kg. Findings in the pancreas were evident in the 4-week minipig study and in the 26-week monkey study. In the exocrine pancreas, degranulation (monkeys) and vacuolation (minipigs) of cells have been related to the affected general health condition of the animals. This was partly associated with necrosis in minipigs at 15.0 mg/kg, when animals died or were sacrificed early due to poor condition consequent to GI problems. The etiology and toxicological relevance of an increased incidence of pancreatic islet cell degeneration in the 26-week monkey study at 5.0 mg/kg is unknown; there were no similar findings in all the other studies, including all species. Evaluation of clinical pathology parameters revealed increases in neutrophils at ≥ 1.5 mg/kg in rats, minipigs and monkeys, which suggests a relationship to inflammatory changes, generally secondary to immunosuppression. Increases in red blood cell parameters (packed cell volume, hemoglobin, and erythrocyte counts) were evident in rats at ≥ 0.5 mg/kg, whereas decreases in

Key safety findings (from non-clinical studies)	Relevance to human usage
	these parameters were noted in monkeys at ≥ 1.5 mg/kg. In view of the absence of corresponding effects on bone marrow, their toxicological importance is doubtful. Decreased platelet counts were observed in most species at ≥ 0.5 mg/kg, but not in monkeys. An increase in fibrinogen concentrations was noted in minipigs and monkeys at ≥ 1.5 mg/kg. Cholesterol was increased in most species at ≥ 0.5 mg/kg. In the 4-week minipig study, effects on lipid metabolism consisted of a slight increase in low-density lipoproteins (LDL) and a slight decrease in high-density lipoproteins. In renal transplant patients treated with sirolimus (rapamycin), hyperlipidemia was suggested to be the result of a reduced catabolism of apoB100-containing lipoproteins (Hoogeveen et al 2001). Low serum albumin in all species associated with a decrease in the albumin/globulin ratio in mice, minipigs and monkey, generally at higher dosages of ≥ 5 mg/kg, may be at least in part related to the nutritional status of the animals or to inflammatory changes in the gut as observed in minipigs and monkeys. The etiology of decreases in serum phosphorus in minipigs at ≥ 1.5 mg/kg and in monkeys at ≥ 0.5 mg/kg is unknown.
Reproductive toxicity	Reproductive and embryofetal development toxicity was evaluated in male fertility studies in rats, female infertility and embryofetal development studies in rats, an embryofetal development study in rabbits. The oral fertility dose-range finding study in male rats revealed effects on spermatogenesis at 1.5 mg/kg, but there were no male-mediated effects on progeny. Males at 5.0 mg/kg showed marked histopathological changes in the testes (atrophy with germ cell depletion) and epididymides (oligospermia to aspermia). In the female reproductive toxicity studies in rats, everolimus did not affect female infertility, but resulted in increases in pre-implantation loss at oral doses of ≥ 0.1 mg/kg (approximately 4% of the AUC0-24 in patients receiving the 10 mg daily dose). Everolimus crossed the placenta and was toxic to the conceptus. The majority of malformations in the treated animals affected thoracic vertebrae, ribs, and sternebrae. In rabbits effects on the embryofetal development were limited to a slight increase in the percentage of late resorptions. It is recommended that women of child-bearing potential should use highly effective contraceptives during treatment. Male patients should not be prohibited from attempting to father a child.
Developmental toxicity	Developmental toxicity was evaluated in a peri- and postnatal development study in rats, neonatal and juvenile study in rats, and a juvenile study in monkeys. In pre- and postnatal development study in rats, the effects observed were limited to slightly reduced body weight and survival in the F_1 generation at ≥ 0.1 mg/kg that did not indicate a specific toxic potential.

Key safety findings (from non-clinical studies)	Relevance to human usage
	In a rat oral juvenile development study, the administration of everolimus at 0.15, 0.5, and 1.5 mg/kg or rapamycin at 1.5 mg/kg on postpartum days 7 to 70 with 13- and 26-week recovery periods resulted in systemic toxicity at all doses, including reduced absolute body weight gain and food consumption, and delayed attainment of some developmental landmarks (e.g. delayed eye opening, delayed reproductive development in both males and females), with full or partial recovery after cessation of dosing. Increased latency time during learning and memory phases in male rats were observed at doses as low as 0.5 mg/kg/day. These observations are considered a general delay of growth and development and not specifically neurodevelopmental toxicity. In juvenile monkeys (approximately 1-year-olds), the oral treatment with everolimus at dosages up to 0.5 mg/kg for 4 weeks did not cause relevant toxicity.
Nephrotoxicity	Kidney lesions as reported for immunosuppressive compounds inhibiting calcineurin pathways were not observed with everolimus. Renal tubular degeneration in CD-1 mice after 13 weeks of treatment at ≥ 5 mg/kg was possibly related to the exacerbation of pre-existing interstitial inflammation, possibly as a consequence of immunosuppression and/or an impaired regeneration of renal lesions as reported for rapamycin (Lieberthal et al 2001). There was no indication of kidney toxicity in mice after life-long treatment up to 0.9 mg/kg. In rats, incidence and severity of lipofuscin in renal tubular epithelial cells was more pronounced in treated animals at ≥ 0.3 mg/kg than in controls of the oncogenicity study, and occurred already after 26 weeks of treatment at ≥ 0.5 mg/kg. The incidence and severity of lipofuscin in renal tubular epithelial cells points to an increased degradation of membrane phospholipids and an acceleration of a normal, age-related process. Increased incidence of hydronephrosis was observed in male rats at ≥ 0.5 mg/kg in the 26-week study. Increased incidence of hydronephrosis was observed in a small number of male rats at ≥ 0.5 mg/kg in the 6-month study. These were considered reversible and were not seen in rats of the 2-year carcinogenicity study at doses up to 0.9 mg/kg.
Hepatotoxicity	There is no evidence of hepatotoxicity in animal studies.
Genotoxicity	In the genotoxicity studies (in vitro: Ames test, chromosomal aberration test with Chinese hamster ovarian cells, mouse lymphoma test; in vivo: mouse micronucleus test), there was no evidence of mutagenic or clastogenic activity. Everolimus exposure in the mouse at the doses used in the micronucleus assay was well in excess of that expected at therapeutic doses in humans.
Carcinogenicity	The oncogenic potential of everolimus was investigated in mouse and rat studies at daily dosages up to 0.9 mg/kg over 104 weeks.

Key safety findings (from non-clinical studies)	Relevance to human usage
	In the mouse carcinogenicity study, there was no indication of a tumorigenic potential up to the high dose of 0.9 mg/kg, corresponding to a factor of 5.4 based on body weight (assuming 60 kg body weight for human), a factor of 0.5 based on BSA, and a systemic exposure ratio of 4.3 relative to a dose of 10 mg/day for man. In the rat carcinogenicity study, there was no indication of a tumorigenic potential up to the high dose of 0.9 mg/kg, which corresponded to a factor of 5.4 based on body weight (assuming a 60 kg body weight for human), a factor of 0.9 based on BSA, and a systemic exposure ratio of 0.2 relative to a dose of 10 mg/day for man.
Safety pharmacology	
Cardiovascular (including potential for QT interval prolongation) Nervous system Respiratory system	Studies related to safety pharmacology showed that everolimus was devoid of relevant effects on vital functions including the cardiovascular function, respiratory function, and nervous systems. Everolimus had no influence on QT interval prolongation as shown with isolated sheep cardiac Purkinje fibers in stable transfected HEK293 cells (hERG currents); and with conventional ECG monitoring in minipigs, and monkeys.
Mechanisms for drug interactions	The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man is CYP3A4. Everolimus is also a moderate inhibitor of PgP-like mediated efflux. Thus, drug-drug interactions (DDI) between everolimus and other substrates, inhibitors, and inducer of CYP3A4 and PgP are possible. In-vitro data suggest everolimus could inhibit the hepatic organic anion transporting polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3). Potential interactions with co-medications whose pharmacokinetics are influenced by OATP activity are possible in the clinic provided that high enough concentrations of everolimus are achieved in vivo.
Other toxicity-related information or data	None

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Duration and exposure by indication in the Oncology setting (RCC, pNET, Lung and GI NET, BREAST) at 10 mg/day (monotherapy or in combination therapy) and in the TSC setting at a starting dose of 3 mg/m^2/day or 4.5 mg/m^2/day, or at 10 mg/day monotherapy are summarized below.

Cumulatively, from the Development International Birth Date (DIBD) to the Data Lock Point (DLP), of 31-Mar-2024, 12,384 patients received everolimus treatment in Novartis-sponsored investigational interventional clinical trials. In the oncology setting, 11,529 patients received everolimus treatment and in the TSC setting, 855patients received everolimus treatment.

Estimates of the cumulative patient exposure, based upon actual exposure data from completed clinical trials and the enrollment and randomization schemes for ongoing trials is provided in Table 4-1.

Table 4-1 Cumulative subject exposure from completed and ongoing clinical trials in the oncology and TSC setting

Exposure	Oncology N (%)	TSC N (%)	Total N (%)
Completed studies	11,468 (92.8.3%)	853 (6.7%)	12,321 (99.5%)
Ongoing studies	61 (0.5%)	2 (0.0%)	63 (0.5%)
Total	**11,529 (93.1%)**	855 (6.9%)	**12,384 (100%)**

N=Number of subjects
Source: Afinitor PSUR (01-Apr-2022 to 31-Mar-2024)- Table 5-1; Afinitor Votubia PSUR (01-Apr-2022 to 31-Mar-2024) – Table 5-1
Note: The exposure pool was updated (MAPs/PSDS were excluded), hence the exposure numbers dropped.

Pooled Oncology setting:

Novartis continues to estimate cumulative patient exposure based upon actual exposure data from selected clinical trials in Oncology indications, which are also used to provide CT data for analysis of safety risks. The selection criteria are:

- Novartis-sponsored interventional CTs with a study population that belong to an approved indication in the oncology setting are included in a pooling when a study reached at least one database lock (DBL) and a finalized Clinical Study Report (CSR) (Section 7) from DIBD to 27-May-2024; and
- If multiple DBLs are reached, the data from the most recent DBL (defined as data cut-off) are included in the pooling.

Twelve CTs (CRAD001C2222, CRAD001C2239, CRAD001C2240, CRAD001C2324, CRAD001C2325, CRAD001L2101, CRAD001L2201, CRAD001L2202, CRAD001L2404, CRAD001T2302, CRAD001Y2301, and CRAD001Y2201) were included in the data pool as

of 09-May-2024. The pooling includes data from any patient who received at least one dose of study treatment and had a valid post-baseline safety assessment (defined as the safety set).

Table 4-2 summarizes number of patients distributed by double-blind phase everolimus and double-blind phase with placebo/active comparator arm. Data from following seven studies was included: CRAD001C2324, CRAD001C2325, CRAD001T2302, CRAD001C2240, CRAD001Y2301, CRAD001C2222 and CRAD001Y2201.

In these seven CTs 1,792 everolimus-treated patients have been exposed to everolimus cumulatively for approx. 1,405.13Patient Treatment Years (PTY).

Table 4-2 Duration of exposure (Pooled Oncology setting)

	Double-blind Everolimus N=1,792	**Double-blind Placebo/active comparator N=1,190**	**Overall Everolimus (Long-term evaluation) N=3,232**
	n (%)	n (%)	n (%)
Duration of exposure (months)			
Mean (SD)	9.4 (10.34)	7.1 (8.49)	11.0 (12.21)
Median	5.7	3.9	6.4
Q1-Q3	3.0-11.5	2.3-8.3	3.0-13.9
Min-Max	0.1-93.5	0.1-86.5	0.0-93.5
Duration of exposure categories-n (%)			
Less than 1 month	78 (4.4)	58 (4.9)	174 (5.4)
At least 1 month	1714 (95.6)	1132 (95.1)	3058 (94.6)
At least 3 months	1338 (74.7)	757 63.6)	2407 (74.5)
At least 6 months	862 (48.1)	376 (31.6)	1669 (51.6)
At least 12 months	425 (23.7)	203 (17.1)	946 (29.3)
At least 18 months	252 (14.1)	114 (9.6)	600 (18.6)
At least 24 months	154 (8.6)	67 (5.6)	397 (12.3)
At least 36 months	46 (2.6)	14 (1.2)	172 (5.3)
At least 48 months	18 (1.0)	4 (0.3)	76 (2.4)
At least 60 months	9 (0.5)	3 (0.3)	25 (0.8)
At least 72 months	7 (0.4)	2 (0.2)	8 (0.2)
Patient-Treatment-Years	1405.13	704.03	2959.69

SD: Standard Deviation.

Patient-Treatment-Years is the sum of each subject's treatment exposure in years.

Data from following trials are included in the double-blind phase (C2324, C2325, T2302, C2240, Y2301, C2222, Y2201, Y2202) and following in the overall analysis (C2324, C2239, C2325, T2302, C2240, L2101, L2201, L2202, L2404, Y2301, C2222, Y2201, Y2202, DIC03, I2201).

Afinitor PSUR (01-Apr- 2022 to 31- Mar- 2024) - Table 5-2

Exposure in the Oncology setting by age was highest in middle-age patients (i.e. '>55 to ≤65 years'). This pattern of exposure was considered related to the demography of the target population, primarily middle-age and older adults (Section 2.1).

Table 4-3 Exposure by age group and gender (Pooled Oncology setting)

		Double-blind Everolimus N=1,792		Double-blind Placebo/active comparator N=1,190		Overall Everolimus (Long-term evaluation) N=3,232	
Age-group	**Sex**	**Subjects n (%)**	**PTY**	**Subjects n (%)**	**PTY**	**Subjects n (%)**	**PTY**
< 18 year	Male	0	0	0	0	0	0
	Female	0	0	0	0	0	0
	Total	0	0	0	0	0	0
>= 18 year - <= 35 year	Male	13(2.6)	9.39	14(3.5)	13.74	41(2.8)	37.64
	Female	16(1.2)	19.98	10(1.3)	8.90	37(2.1)	34.92
	Total	29(1.6)	29.37	24(2.0)	22.64	78(2.4)	72.55
> 35 year - <= 45 year	Male	46(9.1)	41.83	40(10.0)	33.77	120(8.2)	143.52
	Female	69(5.4)	59.84	60(7.6)	26.25	125(7.1)	121.63
	Total	115(6.4)	101.66	100(8.4)	60.02	245(7.6)	265.14
> 45 year - <= 55 year	Male	106(20.9)	80.63	91(22.8)	56.04	355(24.3)	350.68
	Female	261(20.3)	220.87	172(21.7)	108.68	366(20.6)	340.17
	Total	367(20.5)	301.50	263(22.1)	164.72	721(22.3)	690.85
> 55 year - <= 65 year	Male	173(34.1)	127.23	143(35.8)	81.37	510(35.0)	475.75
	Female	460(35.8)	384.51	308(38.9)	168.15	639(36.0)	577.86
	Total	633(35.3)	511.74	451(37.9)	249.52	1149(35.6)	1053.62
> 65 year - <= 75 year	Male	140(27.6)	100.75	96(24.1)	71.78	353(24.2)	325.36
	Female	344(26.8)	247.10	170(21.5)	95.26	436(24.6)	363.10
	Total	484(27.0)	347.85	266(22.4)	167.04	789(24.4)	688.45
> 75 year	Male	29(5.7)	28.99	15(3.8)	8.54	80(5.5)	79.02
	Female	135(10.5)	84.02	71(9.0)	31.55	170(9.6)	110.06
	Total	164(9.2)	113.00	86(7.2)	40.10	250(7.7)	189.08
Total	Male	507(100.0)	388.82	399(100.0)	265.24	1459(100.0)	1411.96
	Female	1285(100.0)	1016.31	791(100.0)	438.79	1773(100.0)	1547.73
	Total	1792(100.0)	1405.13	1190(100.0)	704.03	3232(100.0)	2959.69

PTY: Patient Treatment Years.

Patient-Treatment-Years (PTY) is the sum of each subject's treatment exposure in years.

Data from following trials are included in the double-blind phase (C2324, C2325, T2302, C2240, Y2301, C2222, Y2201, Y2202) and following in the overall analysis (C2324, C2239, C2325, T2302, C2240, L2101, L2201, L2202, L2404, Y2301, C2222, Y2201, Y2202, DIC03, I2201).

Afinitor PSUR (01- Apr- 2022 to 31- Mar- 2024)- Table 5-3

By sex, patient-year exposure was higher in females during double-blind everolimus exposure due to the BREAST indication Table 4-3.

Exposure by race (Table 4-4) in the Oncology setting was predominantly in Caucasian patients, which represents the countries in which the everolimus clinical development plan (CDP) was generally conducted.

Table 4-4 Exposure by race (Pooled Oncology setting)

	Double-blind Everolimus N=1792		Double-blind Placebo/active comparator N=1190		Overall Everolimus (Long-term evaluation) N=3,232	
	Subjects n (%)	PTY	Subjects n (%)	PTY	Subjects n (%)	PTY
Race						
Caucasian	1407 (78.5)	1081.25	949 (79.7)	585.75	2503 (77.4)	2273.76
Black	39 (2.2)	36.74	24 (2.0)	15.69	66 (2.0)	77.44
Asian	284 (15.8)	241.70	196 (16.5)	93.28	549 (17.0)	507.99
Native American	6 (0.3)	2.04	0 (0.0)		19 (0.6)	20.47
Pacific islander	2 (0.1)	1.78	1 (0.1)	0.83	3 (0.1)	3.64
Other	50 (2.8)	39.41	19 (1.6)	8.01	87 (2.7)	73.88
Missing	4 (0.2)	2.21	1 (0.1)	0.48	5 (0.2)	2.51
Total	1792 (100.0)	1405.13	1190 (100.0)	704.03	3232 (100.0)	2959.69

PTY: Patient Treatment Years.

Patient-Treatment-Years (PTY) is the sum of each subject's treatment exposure in years.

Data from following trials are included in the double-blind phase (C2324, C2325, T2302, C2240, Y2301, C2222, Y2201, Y2202) and following in the overall analysis (C2324, C2239, C2325, T2302, C2240, L2101, L2201, L2202, L2404, Y2301, C2222, Y2201, Y2202, DIC03, I2201).

Afinitor PSUR (01 Apr 2022 to 31 Mar 2024)- Table 5-4

Pooled TSC setting

Novartis continues to estimate cumulative patient exposure based upon actual exposure data from clinical trials as described in the rules below:

- Novartis - sponsored interventional clinical trials with a study population belonging to an approved indication in the TSC setting are included in a pooling when a study reached at least one database lock (DBL) and a Finalized Clinical Study Report (CSR).
- If multiple DBLs are reached, the data from the most recent DBL [defined as data cut-off (DCO)] are included in the pooling.

Four clinical studies (CRAD001C2485, CRAD001M2301, CRAD001M2302 and CRAD001M2304) are included in the data pool as of DLP of 31-Mar-2020 based on the above criteria. The pooling includes data from any patient who received at least one dose of double-

blind or open-label everolimus treatment and had a valid post-baseline safety assessment [defined as the Safety Set].

The characteristics of patients (including age, gender, and race distribution) exposed to everolimus and comparator treatments in those studies are discussed below, in light of the expected characteristics of the target population for the indication. There are no Novartis-sponsored investigational clinical trials in healthy volunteers [subjects] in the TSC setting.

In the four studies (CRAD001C2485, CRAD001M2301, CRAD001M2302 and CRAD001M2304), 612 patients have been exposed to everolimus cumulatively for approximately 1,760 Patient-Treatment-Years (PTY) (Table 4-5).

Table 4-5 Duration of Exposure (Pooled TSC setting)

Duration of exposure	***Double-blind Everolimus N=404 Patient's n (%)**	***Double-blind Placebo N=197 Patient's n (%)**	****Overall Everolimus (Long-term evaluation) N=612 Patient's n (%)**
Duration of exposure (months)			
Mean (SD)	7.3 (5.01)	6.8 (4.52)	34.5 (16.80)
Median	4.3	4.2	36.8
Q1-Q3	4.1-10.1	4.1-9.1	24.9-46.7
Min-Max	0.5-26.5	0.5-26.4	0.5-83.2
Duration of exposure categories-n (%)			
Less than 1 month	7 (1.7)	1 (0.5)	8 (1.3)
At least 1 month	397 (98.3)	196 (99.5)	604 (98.7)
At least 3 months	391 (96.8)	191 (97.0)	592 (96.7)
At least 6 months	149 (36.9)	68 (34.5)	564 (92.2)
At least 12 months	73 (18.1)	26 (13.2)	522 (85.3)
At least 18 months	17 (4.2)	6 (3.0)	500 (81.7)
At least 24 months	4 (1.0)	1 (0.5)	469 (76.6)
At least 36 months	0 (0.0)	0 (0.0)	320 (52.3)
At least 48 months	0 (0.0)	0 (0.0)	119 (19.4)
At least 60 months	0 (0.0)	0 (0.0)	31 (5.1)
At least 72 months	0 (0.0)	0 (0.0)	7 (1.1)
PTYs	**246**	**112**	**1,760**

DLP: Data Lock Point, N (n): Number, PSUR: Periodic Safety Update Report, PTY: Patient-Treatment-Years, SD: Standard deviation, TSC: Tuberous Sclerosis complex.

PTY is the sum of each subject's treatment exposure in years. Data from following trials are included in the double-blind phase (M2301, M2302, and M2304) and the following in the overall analysis (M2301, M2302, M2304, and C2485).

*Double-blind phase: Patients receiving everolimus or placebo during the double-blind treatment phase.

**Long-term evaluation phase: Patients receiving everolimus during double-blind and/or open-label phases.

Afinitor Votubia PSUR (01-Apr-2022 to 31-Mar-2024) – Table 5-2

Exposure by age and sex

The pattern of exposure by age and by sex is consistent with the demography of the target populations for the currently approved indications in the TSC setting. They include younger than 18-year-old (pediatric) and older (adult) patients from both sexes (Table 4-6).

The cumulative exposure in adult patients (≥18-year-old) was at approximately 620 PTY. The cumulative pediatric exposure predominantly in 3-year-old to less than 12-year-old patients was at 709 PTY. By sex, there were more female adult patients than male adult patients. Furthermore, the youngest pediatric patients tended to be male (Table 4-6).

Table 4-6 Exposure by age group and sex (Pooled TSC-setting)

Sex	Age-group	*Double-blind everolimus N=404		*Double-blind placebo N=197		**Overall Everolimus (Long-term evaluation N=612	
		Patients N (%)	PTY	Patients N (%)	PTY	Patients N (%)	PTY
Female	< 1 year	0	0	0	0	0	0
	≥ 1 year to < 2 years	3 (1.5)	3.4	4 (3.8)	3.3	3 (1.0)	13.0
	≥ 2 years to < 3 years	8 (4.0)	3.2	3 (2.9)	1.3	10 (3.3)	26.1
	≥ 3 years to < 12 years	80 (40.2)	41.5	38 (36.2)	19.2	122 (40.1)	333.8
	≥ 12 years to < 18 years	30 (15.1)	13.5	19 (18.1)	11.1	54 (17.8)	150.4
	< 18 years	121 (60.8)	61.6	64 (61.0)	34.8	189 (62.2)	523.2
	≥ 18 years to ≤ 65 years	78 (39.2)	61.8	41 (39.0)	28.0	115 (37.8)	360.0
	> 65 years to ≤ 75 years	0	0	0	0	0	0
	> 75 years	0	0	0	0	0	0
	Total (Female)	**199 (100.0)**	**123.4**	**105 (100.0)**	**62.8**	**304 (100.0)**	**883.2**
Male	< 1 year	0	0	2 (2.2)	1.6	0	0
	≥ 1 year to < 2 years	5 (2.4)	5.3	1 (1.1)	0.3	7 (2.3)	22.8
	≥ 2 years to < 3 years	13 (6.3)	8.9	7 (7.6)	2.4	18 (5.8)	51.6
	≥ 3 years to < 12 years	89 (43.4)	41.5	39 (42.4)	15.0	136 (44.2)	374.9

Sex	Age-group	*Double-blind everolimus N=404		*Double-blind placebo N=197		**Overall Everolimus (Long-term evaluation N=612	
		Patients N (%)	**PTY**	**Patients N (%)**	**PTY**	**Patients N (%)**	**PTY**
	≥ 12 years to < 18 years	43 (21.0)	22.9	17 (18.5)	9.7	59 (19.2)	168.1
	< 18 years	150 (73.2)	78.6	66 (71.7)	29.0	220 (71.4)	617.4
	≥ 18 years to ≤ 65 years	55 (26.8)	44.1	26 (28.3)	20.5	88 (28.6)	259.6
	> 65 years to ≤ 75 years	0	0	0	0	0	0
	> 75 years	0	0	0	0	0	0
	Total (Male)	**205 (100.0)**	**122.7**	**92 (100.0)**	**49.5**	**308 (100.0)**	**877.0**
Male and Female	≥ 3 years to < 12 years	169 (41.8)	83.0	77 (39.1)	34.1	258 (42.2)	709
	< 18 years	271 (67.1)	140.2	130 (66.0)	63.9	409 (66.8)	1140.5
	≥ 18 years	133 (32.9)	105.9	67 (34.0)	48.5	203 (33.2)	619.6
	Grand Total	**404 (100.0)**	**246**	**197 (100.0)**	**112**	**612 (100.0)**	**1,760**

DLP: Data Lock Point, N: Number, PSUR: Periodic Safety Update Report, PTY: Patient-Treatment-Years, TSC: Tuberous Sclerosis complex

PTY is the sum of each subject's treatment exposure in years. Data from following trials are included in the double-blind phase (M2301, M2302, and M2304) and the following in the overall analysis (M2301, M2302, M2304, and C2485).

*Double-blind phase: Patients receiving everolimus or placebo during the double-blind treatment phase.

**Long-term evaluation phase: Patients receiving everolimus during double-blind and/or open-label phases.

Afinitor Votubia PSUR (01-Apr-2022 to 31-Mar-2024) – Table 5-3

Exposure by race

The cumulative exposure to everolimus by race was predominantly to Caucasian patients at approximately 1,367 PTY (Table 4-7).

Table 4-7 Exposure by race (Pooled TSC setting)

	*Double-blind Everolimus N=404		*Double-blind Placebo N=197		**Overall Everolimus (Long-term evaluation) N=612	
Race	**Patient's n (%)**	**PTY**	**Patient's n (%)**	**PTY**	**Patient's n (%)**	**PTY**
Caucasian	304 (75.2)	206.0	148 (75.1)	93.2	460 (75.2)	1366.9
Asian	67 (16.6)	25.4	31 (15.7)	12.1	97 (15.8)	253.5
Black	6 (1.5)	3.7	2 (1.0)	0.8	10 (1.6)	33.6
Pacific islander	2 (0.5)	1.5	0	0	2 (0.3)	5.8
Native American	1 (0.2)	0.3	0	0	1 (0.2)	2.9
Other	24 (5.9)	9.3	16 (8.1)	6.1	42 (6.9)	97.5
Total	**404 (100.0)**	**246**	**197 (100.0)**	**112**	**612 (100.0)**	**1,760**

DLP: Data Lock Point, N: Number, PSUR: Periodic Safety Update Report, PTY: Patient-Treatment-Years, TSC: Tuberous Sclerosis complex

PTY is the sum of each subject's treatment exposure in years. Data from following trials are included in the double-blind phase (M2301, M2302, and M2304) and the following in the overall analysis (M2301, M2302, M2304, and C2485).

*Double-blind phase: Patients receiving everolimus or placebo during the double-blind treatment phase.

**Long-term evaluation phase: Patients receiving everolimus during double-blind and/or open-label phases.

Afinitor Votubia PSUR (01-Apr-2022 to 31-Mar-2024) – Table 5-4

Exposure by special population (Pediatric patients)

In the four clinical trials (RAD001C2485, CRAD001M2301, CRAD001M2302 and CRAD001M2304), a total of 409 pediatric patients (Table 4-8) were exposed to everolimus at about 1140 PTY (about 75% of the total cumulative exposure; Table 4-6). As previously stated, the highest exposure (709 PTY) in any pediatric age group occurred in patients being 3-year-old to less than 12-year-old. The cumulative exposure to everolimus in the 38 pediatric patients being less than 3-year-old was 113 PTY.

Table 4-8 Exposure by age and sex (Pediatric patients) (Pooled TSC setting)

Age-group	Female		Male		Total	
	Patients N (%)	PTY (%)	Patients N (%)	PTY (%)	Patients N (%)	PTY (%)
< 1 year	0	0	0	0	0	0
≥ 1 year to < 2 years	3 (1.6)	13 (2.5)	7 (3.2)	22.8 (3.7)	10 (2.5)	35.7 (3.1)
≥ 2 years to < 3 years	10 (5.3)	26.1 (5.0)	18 (8.2)	51.6 (8.4)	28 (6.8)	77.6 (6.8)
≥ 3 years to < 12 years	122 (64.5)	333.8 (63.8)	136 (61.8)	374.9 (60.7)	258 (63.1)	708.6 (62.1)
≥ 12 years to < 18 years	54 (28.6)	150.4 (28.7)	59 (26.8)	168.1 (27.2)	113 (27.6)	318.5 (27.9)

Age-group	Female		Male		Total	
	Patients N (%)	PTY (%)	Patients N (%)	PTY (%)	Patients N (%)	PTY (%)
Total	189 (100)	523 (100)	220 (100)	617 (100)	409 (100)	1,140 (100)

DLP: Data Lock Point, N: Number, PSUR: Periodic Safety Update Report, PTY: Patient-Treatment-Years, TSC: Tuberous Sclerosis complex.

PTY is the sum of each subject's treatment exposure in years. Data from following are included in the analysis (M2301, M2302, M2304, and C2485).

Afinitor Votubia PSUR (01-Apr-2022 to 31-Mar-2024) – Table 5-5

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Known active substance hypersensitivity	Patients predisposed to or with known prior history of mTOR inhibitor hypersensitivity may experience symptoms including, but not limited to: anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment)	No	This criteria is included as contraindication for everolimus therapy.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women Breastfeeding women	There are no adequate data from the use of everolimus in the clinical studies with pregnant or breast-feeding women
Patients with relevant comorbidities: • Patients with 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, respectively, with impaired hepatic function relative to subjects with normal hepatic function. 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.

Type of special population	Exposure
	In a second study of 34 subjects with different grades of 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. AUC0-inf) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively. Dose recommendations for patients with hepatic impairment are provided in the SmPc based on the results of these two studies.
Patients with renal impairment	Impaired renal function is not expected to influence everolimus pharmacokinetics based on the fact that ≤5 percent of radioactivity was excreted in urine in the mass balance study in maintenance renal transplant patients CP study W107 In the population pharmacokinetic analyses, in 170 patients with advanced cancer no significant influence of creatinine clearance (25 - 178 mL/min) was detected on CL/F of everolimus [Everolimus Modeling Report Population pharmacokinetics (PK)] and [Errata to Everolimus Modeling Population PK Report]. On this basis, no dose adjustment is necessary for patients with renal impairment.
Immunocompromised Patients	None
Patients with Underlying or ongoing infection	None
Population with relevant different ethnic origin	Although limited, safety information from the current CDP does include ethnicity as categorized by Hispanic / Latino, Chinese, and mixed ethnicity; and by race predominantly in Caucasian patients categorized as 'other' and Asian patients categorized as Chinese and Japanese in the double-blind Oncology setting (Table 4-4). No safety concerns were observed based on differences in race or ethnicity in oncology setting. Analyses by race and ethnicity (Table 4-7) affirmed extensive long-term exposure to everolimus in the TSC setting (ICH 1998). However, exposure was low (Asian, Hispanic / Latino, and Chinese) or absent (Native American and Indian) when compared to that in the Oncology setting (Table 4-4). • 460 Caucasian patients were exposed to long-term everolimus with 1366.9 PTY; 97 Asian patients with 253.5 PTY; 10 black patients, 33.6 PTY; 2 Pacific Islander patient, 5.8 PTY: all in the TSC setting • All remaining races were categorized as 'other' with 97.5 PTY. No safety concerns were observed based on differences in race or ethnicity in TSC setting
Other **Children**	Currently, there are no patients in the Oncology CDP less than 18 years (Table 4-3). Analyses by age groups that include children are adequately described under Section 4.1 in the TSC setting.
Elderly (> 75 years old)	Long-term exposure to everolimus in geriatrics includes 247 patients for an exposure of 174.82 PTY (Table 4-3). Although limited, safety information from the current CDP does include up to 81 male patients and 166 female patients for a total of 70.70 PTY and 104.12 PTY, respectively, in the open-label Oncology setting: all older than 75 years (Table 4-3). There is no patient older than 75 years in the pooled TSC setting (Table 4-6).

Type of special population	Exposure
Source: RMP version 13.1 - Table 5-2	

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 V.1.1 Method used to calculate exposure

As of 31-Mar-2024 (RMP DLP), in countries of the European Economic Area (EEA), CCI everolimus is licensed under brand name 'Votubia' for TSC indications, whereas in all other countries [Rest of the World (ROW)] it is licensed under brand name 'Afinitor' for both TSC and Oncology indications.

Hence, it is impossible to distinguish between the use of everolimus (and corresponding sales) for TSC and Oncology indications in ROW countries. In order to generate reasonable estimates of use (sales) data for Afinitor® in TSC indications in ROW countries, it was assumed that the use pattern in these countries was comparable to those in the EEA, CCI which offer everolimus as Afinitor® for Oncology and Votubia® for TSC indications.

The ratio of tablets sold cumulatively for TSC (Votubia®) versus Oncology indications (Afinitor®) in the EEA, CCI (all dose strengths considered) was extrapolated to all other individual countries (ROW) following approval for TSC, which enabled the calculation of exposure estimations in the TSC setting in these countries and thus globally. As for the previous PSUR reporting intervals, this methodology supported the estimation (calculation) of everolimus exposure data stratified by dose strength and region in both Oncology and TSC setting.

6.1.2 Part II Module SV.1.2. Exposure

Non-study post-authorization exposure is summarized by Oncology and TSC settings, region, and by dosing strengths as indicated in Table 6-1.

The total cumulative worldwide patient exposure (until 31-Mar-2024) in oncology setting is estimated at 270,932 PTY and in the TSC indications is estimated to approximately 75,110 PTY.

Table 6-1 Cumulative exposure from marketing experience by setting, region, and dosing strength, estimated cumulative exposure in the Oncology and TSC settings: IBD to DLP

Dose strength of tablet (also daily therapeutic dose per patient)	Units sold (tablets)	Estimated exposure (PTY)
Oncology Setting		
EEA countries, CCI		
2.5 mg	2,001,305	5,483
5 mg	16,452,469	45,075

Dose strength of tablet (also daily therapeutic dose per patient)	Units sold (tablets)	Estimated exposure (PTY)
Oncology Setting		
7.5 mg	16,576	45
10 mg	21,852,179	59,869
ROW*		
2.5 mg	1,611,380	4,415**
5 mg	27,536,688	75,443**
7.5 mg	1,993,430	5,461**
10 mg	27,426,317	75,141**
Total	**98,890,345**	**270,932**
TSC Setting		
EEA countries, CCI		
2.5 mg	3,231,436	8,853
5 mg	3,971,272	10,880
10 mg	1,443,027	3,953
Dispersible Tablets (2 mg, 3 mg, and 5 mg)	3,055,110	8,370
ROW*		
2.5 mg	2,708,928	7,422**
5 mg	6,444,625	17,657**
10 mg	1,847,566	5,062**
Dispersible Tablets (2 mg, 3 mg, and 5 mg)	4,713,152	12,913
Total	**27,415,116**	**75,110**

EEA: European Economic Area; mg: milligram; PSUR: Periodic Safety Update Report; PTY: Patient-Treatment-Year; ROW: Rest Of the World; TSC: Tuberous Sclerosis Complex.

This table includes cumulative data obtained until Mar 2024.

CCI PSUR (01 Apr 2017 to 31 Mar 2021), CCI

CCI

Dose strength of tablet (also daily therapeutic dose per patient)	Units sold (tablets)	Estimated exposure (PTY)
Oncology Setting		
CCI		

Note: The values in above table are calculated by using formulae in excel. The sum up values may not match with the total as the figures are rounded off.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action of everolimus, a potential for abuse and dependence is not anticipated.

The potential for misuse for illegal purposes is considered negligible as everolimus is only available by prescription.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Afinitor has been marketed since 03-Mar-2009 in the US and 03-Aug-2009 in the EU. Votubia has been marketed since 29-Oct-2010 in the US and 02-Sep-2011 in the EU. The current approved RMP v15.0 does not include any outstanding safety concern in the oncology setting whereas the safety concerns of "Female infertility", "Postnatal developmental toxicity", "Male infertility", "Long-term safety" and "Neurocognitive and sexual development in pediatric patients" were retained and remained open in the TSC setting. Study CRAD001M2305, which was a PASS study as well as an RMP commitment aimed to address the safety concerns of "Postnatal developmental toxicity", "Long-term safety" and "Neurocognitive and sexual development in pediatric patients" was completed and final CSR was published in 27-May-2024. No new significant safety information emerged from this study. No other additional PV and risk minimization activities are ongoing for these safety concerns.

In addition, in the assessment report for Afinitor/Votubia RMP v15.0 (Procedure No. EMEA/H/C/WS1923), the PRAC recommended the removal of "Female infertility" and "Male infertility" from the list of safety concerns in the TSC setting in the next RMP. No additional PV and risk minimization activities are ongoing for these safety concerns.

Therefore, with this RMP update, Novartis proposes to remove all outstanding safety concern/risks in the TSC setting, considering that all of the risks have been well characterized/adequately described in the SmPC. These are adequately managed according to the standards of clinical practice. Additionally, no new safety information has arisen from the study CRAD001M2305.

The safety concerns that were removed or reclassified since the previous RMP version were presented in Table 8-1:

Table 8-1 Status of safety concerns with the submission of the updated RMP

Risk	Status	Risk retained	
		Oncology setting	TSC setting
Identified Risks			
Female fertility (including secondary amenorrhea) (TSC setting only)	Removed	NA	No
Potential Risks			
Postnatal developmental toxicity (TSC setting only)	Removed	NA	No

Risk	Status	Risk retained	
		Oncology setting	TSC setting
Male infertility (TSC setting only)	Removed	NA	No
Missing information			
Long-term safety (TSC setting only)	Removed	NA	No
Neurocognitive and sexual development in pediatric patients (TSC setting only)	Removed	NA	No

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

None.

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

All the important identified risks, important potential risks and missing information were removed.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

None for the purpose of the RMP.

Other forms of routine pharmacovigilance activities

Not Applicable.

10.2 Part III.2. Additional pharmacovigilance activities

None.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for post-authorization efficacy studies (PAES).

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Given the absence of any risks in the current RMP, no risk minimization measures are required.

13 Part VI: Summary of the risk management plan for Afinitor and Votubia (everolimus)

This is a summary of the risk management plan (RMP) for Afinitor and Votubia. There are no important identified risks, important potential risks and missing information for Afinitor and Votubia.

Afinitor and Votubia's summary of product characteristics(s) (SmPCs) and their package leaflets give essential information to healthcare professionals and patients on how Afinitor and Votubia should be used.

This summary of the RMP for Afinitor and Votubia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, of all which is part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of Afinitor and Votubia's RMP.

13.1 Part VI: I. The medicine and what it is used for

Afinitor and Votubia contains everolimus as the active substance and is it used in the following indications:

Oncology setting

- Renal cell carcinoma [RCC], which is for the treatment of patients with advanced renal cell carcinoma whose disease has progressed on or after treatment with VEGF-targeted therapy
- Neuroendocrine tumors of pancreatic origin [pNET], which is for the treatment of patients with unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors of pancreatic origin in adults with progressive disease
- Hormone receptor-positive advance breast cancer [BREAST], which is 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 tumors of gastrointestinal (GI) or lung origin [NET], which is for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumors of GI or lung origin in adults with progressive disease

TSC setting

- Subependymal giant cell astrocytoma (SEGA) associated with TSC [TSC-SEGA], which is for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not amendable to surgery. The evidence is based on an analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated
- Renal angiomyolipoma associated with TSC [TSC-AML], which is for the treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors), but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume

- Refractory seizures associated with TSC [TSC-Seizures], which is for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC

Further information about the evaluation of Afinitor and Votubia's benefits can be found in Afinitor and Votubia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/afinitor

https://www.ema.europa.eu/en/medicines/human/EPAR/votubia

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Not applicable as there are no identified risks, important potential risks and missing information for Afinitor and Votubia.

13.2.1 Part VI: II.A: List of important risks and missing information

All the important identified risks, important potential risks and missing information were removed.

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

13.2.2 Part VI: II.B: Summary of important risks

Not applicable, since there are no important identified risks, nor important potential risks or missing information.

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Afinitor/Votubia.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Afinitor/Votubia.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

There are no proposed additional risk minimization activities.