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Regulatory Affairs

Afinitor® (Everolimus)

Summary of the Risk Management Plan (RMP) for Afinitor® (Everolimus)

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1 Summary of the Risk Management Plan (RMP) for Afinitor® (everolimus)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Afinitor® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the „Arzneimittelinformation“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. This summary relates to the RMP version shared with Swissmedic in June 2017 (EU RMP 13.0/13.0 from Feb 2017).

Please note that the reference document which is valid and relevant for the effective and safe use of Afinitor in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Afinitor.

2 Overview of disease epidemiology

Oncology setting

Renal cell carcinoma (RCC) is a type of kidney cancer. It occurs more often in Europe and North America than in Asia and Africa. In the EU, about 3 to 4 people in 10000 have RCC. It has been estimated that over 170000 in the EU and over 190000 people in the US have RCC. RCC occurs about twice as often in men as in women. It is usually diagnosed between 60 and 65 years of age. It has been reported that between 5% and 90% of patients with RCC survive 5 years after diagnosis depending on stage of the disease.
Neuroendocrine tumors (NETs) are a rare type of cancer. NETs arise in neuroendocrine cells of pancreas, stomach, the small intestine and other organs. Every year, over 8 people in 1 million are diagnosed with gastroenteropancreatic NET in Europe. NETs can appear at anytime during a lifetime, but are more often found in older males of the African American population. It has been estimated that over 100000 people in the US have NET. Between 35% and 82% of patients with NET survive 5 years after diagnosis.
NETs start from neuroendocrine cells inside any organ called the stomach, lung, small intestine, appendix, colon, or pancreas. NETs that can release a substance called a hormone are called functional; those that do not release hormones are called non-functional. So, NETs are not always the same. Most (72% to 92%) patients with NET have a tumor that is not functional and not from the pancreas. Each year in Europe, 6244 new patients happen to get NET from the gastrointestinal tract and pancreas with a tumor that is not functional. But, less patients get it from the lung. Each year in Europe, 3148 new patients happen to get NET from the lung. NETs from the gastrointestinal tract happen more often as a patient gets older. NETs from the lung are most often found around 54 years old. NETs from the small intestine are most often found

around 68 years of age. NETs from the small intestine happen more often in males. NETs from the appendix happen more often in females. About half of patients with NET from the gastrointestinal tract or lung live for 5 years after knowing they have this tumor.
Breast cancers in postmenopausal women are most often diagnosed in the early sixties. Every year, about 39 women in 100000 women population are diagnosed with breast cancer worldwide. The incidence is higher in Europe (104 in 100000) and in the US (124 in 100000). Breast cancer is 100 times less frequent in men than in women. In the US, the overall 5-year relative survival for 2001 thru 2007 was 89.1%.

TSC Seizures
Tuberous sclerosis complex, TSC, is a genetic disease and that means it runs in the family.
In TSC, every cell in the body contains a gene mutation that came from a parent. Some cells in the body contain a second mutation that occurred by chance during the growth and division of the cell. When this occurs, unusual growth of cells happens in most patients. There are times when the unusual growth happens in the brain or kidney. These types of TSC patients are talked about below.
Most TSC patients have epilepsy and many are autistic or mentally retarded. This may occur because of the mutation that came from a parent or the presence of two mutations in some cells. Regardless of the reason, sometimes TSC patients have seizures. Seizures are hard to control. Seizures are a burden to a patient and their family. A lot of patients are children. As these children grow, the nerves in their brain do not work like they should.
There are drugs (AEDs) that can control seizures, but these drugs often do not work well in TSC-associated epilepsy.

TSC setting

Subependymal giant cell astrocytomas (SEGA) is a non-cancerous brain tumor that is associated with TSC and is found in 5% to 20% of patients with TSC. It is usually diagnosed below 18 years of age. It is estimated that between 4 and 12 people in 1 million have SEGA. In TSC patients, about 25% die due to SEGA.
Renal angiomyolipomas associated with TSC is mostly an adult kidney disease. It is found in 70% to 90% of adult patients with TSC. There is no sex predominance but women have symptoms more often than men. Kidney complications is the most common reason for death in TSC patients.
The average age at death of TSC patients is about 50 years old.

3 Summary of treatment benefits

Oncology and TSC settings
Everolimus was more effective than placebo (sugar pill) at treating patients in all studies either alone or when combined with another drug.
The way in which effectiveness was measured was different for the three cancer conditions compared to the disease TSC. This is because on the one hand, patients with TSC have a non-malignant tumor which can cause problems if it gets too big. It usually does not spread. So, shrinking the TSC tumors is very important to help patients. On the other hand, tumors in cancer

patients are malignant and have already spread in their body. Therefore, cancer patients can benefit from the medication if it allows the patients to live longer without the disease getting worse.

Results in lay language

Oncology setting

In the renal cell carcinoma study, patients who took everolimus lived for an average of 4.9 months without the disease getting worse, compared with 1.9 months for the patients who took placebo.

Surgery for renal cell carcinoma is an option for patients who have early disease that has not spread. Another treatment option is to block the blood supply to the cancer (arterial embolization), which can also be combined with surgery. Radiation is often used to help reduce symptoms, but not as a cure. For patients with advanced disease, and surgery is not able to cure, the first choice for treatment is sunitinib, sorafenib or both (VEGF-inhibitors).

These drugs may block the blood vessels which supply the cancer. If these drugs fail, then the next choice is everolimus which can prevent the cancer from getting worse.

In the pancreatic neuroendocrine study, patients who took everolimus lived for an average of 11 months without the disease getting worse, compared with 4.6 months for the patients who took placebo.

Pancreatic Neuroendocrine Tumors is divided into many different types depending on what hormones the cancer produces and secretes into the blood. These hormones are what can cause the symptoms often seen in these patients. Like other solid cancers, if caught very early, surgery to remove the cancer is the first option. Surgery can also be used to reduce the size of the cancer without curing the patient. Patients who secrete hormones which cause symptoms like flushing of the face and diarrhea can take an anti-hormone treatment called somatostatin analogs (SSA).

The speed at which the cancer is growing is also important. If the cancer is aggressively growing, then the best treatment is chemotherapy (with streptozocin). Treatment with everolimus is an option for those patients who have wide spread disease or who cannot have surgery, but the cancer is not growing aggressively.

Patients with NET from their gastrointestinal tract or lung who took everolimus in a study called CRAD001T2302 lived for about 11 months without their disease getting worse or dying, compared with 3.9 months in patients who took placebo. In other words, the median progression-free survival (PFS) for 205 patients treated with everolimus 10 mg was 11.01 months, compared with 97 patients treated with placebo with a median PFS of 3.91 months. The difference with everolimus was an improvement by 7.10 months.

In the breast cancer study, patients who took everolimus with a hormone drug lived for an average of 7.8 months without their disease getting worse, compared with 3.2 months for the patients who took placebo.

Breast cancer is divided into many different types, depending on whether and what hormones might play a role. If the disease is caught very early, surgery to remove the cancer is the first choice. Surgery might also be used to reduce the size of the cancer before beginning medication for treatment. Depending on the hormone involved, the cancer can be treated with specific anti-hormone drugs. If this fails, then the patient can be treated with an anti-hormone drug (exemestane) in combination with everolimus which helps to slow down the growth of the

cancer. Radiation and chemotherapy can also be used but often to help reduce symptoms or when other treatments failed, and not as a cure.

TSC Seizures
All patients had TSC in this study. Patients and / or caregivers counted the seizures in a diary. These seizures were sensory or motor seizures that had not been previously observed.
There were 366 patients with TSC who took everolimus or the sugar pill (placebo).
There were two ways to show everolimus worked, as measured by primary endpoint of:

- refractory seizure frequency response rate
  33 patients in the 3 to 7 ng/mL-trough everolimus arm and 52 patients in the 9 to 15 ng/mL-trough everolimus arm vs. 18 patients in the placebo arm responded positively to treatment
  Odds ratios were statistically significantly higher in the two everolimus arms vs. placebo: 2.21 ($p=0.008$) and 3.93 ($p<0.001$).
- refractory seizure frequency
  median reduction of seizure frequency per week was 29.29% in the 3 to 7 ng/mL trough everolimus arm and 39.55% in the 9 to 15 ng/mL-trough everolimus arm vs. 14.86% in the placebo arm.
  Reductions in seizure frequency were statistically significantly higher in the two everolimus arms vs. placebo: $p=0.003$ and $p<0.001$.

TSC setting
Everolimus was shown to be effective at treating patients with SEGA and renal angiomyolipoma by shrinking the volume of the tumours. In patients with SEGA, the main brain tumour shrank by half in approximately 30% of patients and by about a third in around 70% of patients. In patients with renal angiomyolipoma, the kidney tumour shrank by at least half in 42% of patients (33 out of 79 patients) treated with everolimus, compared with none of the 39 patients who received placebo.
A group of expert doctors have decided together the best way to treat patients with SEGA or patients with renal angiomyolipoma (Krueger et al 2013). For patients who just got SEGA and have symptoms, surgery and maybe a shunt would be done first. For patients whose SEGA is growing with no symptoms, surgery or a drug called an mTOR inhibitor (like everolimus) is the first treatment given. For patients whose renal angiomyolipoma just started bleeding, the doctor may block the bleeding or give a drug called a corticosteroid as the first thing to do. And, the doctor would do this before taking out the kidney. For patients whose renal angiomyolipoma has grown bigger than the size of a pea, but with no symptoms, the mTOR inhibitor would be given first. For patients with renal angiomyolipoma but no symptoms, the doctor may block the bleeding or take out part of the kidney as a second option.

4 Unknowns relating to treatment benefits

In the main and supporting studies, most patients were Caucasian aged between 52 and 86 years with few patients aged over 65 years. There is no evidence to suggest that results would be any different in non-white patients or in younger patients unable to tolerate high dose chemotherapy.

The treatment benefits in patients with SEGA less than 1 year and patients with refractory seizures and TSC less than 2 years are unknown.

5 Summary of safety concerns

Table 5-1 Important identified risks

Risk	What is known	Preventability
Inflammation of the lungs not caused by an infection (Non-infectious pneumonitis)	About 12% (12 people out of 100) who took everolimus had lung inflammation that was not caused by an infection. Sometimes the lung inflammation was severe and a few people died. The lung inflammation will usually go away after everolimus is stopped. Your doctor might give you a steroid (such as prednisone) to help treat the lung inflammation.	Yes, by monitoring for coughing, shortness of breath, or any other breathing problems.
Severe infections	Everolimus may make it more difficult for your body to fight infections. Therefore, you may be at risk of getting an infection while you are taking everolimus. Some infections have been severe and a few people died. In some patients, the infection leads to lung failure or liver failure.	Yes, by: 1). Making sure that any infection is fully gone before starting everolimus, and 2). Monitoring for any signs and symptoms of an infection (such as fever) while taking everolimus.
Severe allergic reactions (Hypersensitivity (anaphylactic reactions))	Some patients who took everolimus had allergic reactions (shortness of breath, flushing such as redness of the face, chest pain or swelling of the throat or tongue). A few patients had an allergic reaction so severe it caused death.	Yes, by knowing about any allergies (including other medicines or foods) before taking everolimus.
Mouth sores (Stomatitis)	Some patients who took everolimus had mouth sores. Mouthwash that contains alcohol or peroxide may make mouth sores worse and should not be used. Antifungal agents (drugs used to treat an infection caused by a fungus) should not be used unless your doctor has told you that you have a fungal infection.	Yes, by following instructions on oral care (mouth, teeth and gums) while taking everolimus.
Problems with wound healing (Wound healing complications)	Some patients who took everolimus had problems with a wound healing well.	Yes, by reporting any recent surgery or any planned surgery while taking everolimus.

Risk	What is known	Preventability
Increased amount of protein in your blood or urine that tells how well your kidneys are working, and kidney failure (Increased creatinine / proteinuria / renal failure)	Some patients who took everolimus had mild increases in the amount of creatinine in their blood or urine. Some other patients had large increases in the amount of that type of protein in their blood or urine that lead to kidney failure. A few patients died.	Yes, by checking urine and blood before taking everolimus and while taking everolimus to see how well the kidneys are working.
High blood sugar (Hyperglycemia / New onset diabetes mellitus)	If you have diabetes (high level of sugar in your blood), everolimus may increase blood sugar levels and worsen diabetes mellitus. You may need to use insulin or take pills for high blood sugar.	Yes, by: 1). Checking blood sugar levels before starting everolimus and while taking everolimus, and 2). Monitoring for an increase in thirst or an increase in urination.
Abnormal amount of cholesterol and / or fat (triglyceride) in the blood (Dyslipidemia)	Some patients who took everolimus had increased amounts of cholesterol and triglycerides in the blood.	Yes, by checking the cholesterol and other blood fat amounts before starting everolimus and while taking everolimus.
Low amount of phosphate in the blood (Hypophosphatemia)	Some patients who took everolimus had low amounts of phosphate in the blood. The cause of this is unknown.	Yes, by checking the amount of phosphate in the blood before starting everolimus and while taking everolimus.
Heart failure (Cardiac failure)	Some patients who took everolimus had symptoms of heart failure such as breathlessness, difficulty breathing when lying down, and swelling of the feet or legs.	Yes, by monitoring for breathlessness, difficulty breathing when lying down, or swelling of the feet or legs.
Decrease in the number of blood cells such as red blood cells, white blood cells, and platelets (Cytopenia)	Many patients who took everolimus had low blood cell counts.	Yes, by checking the number of red blood cells, white blood cells, and platelets in the blood before starting everolimus and while taking everolimus.
Large loss of blood and bleeding that is hard to control (Hemorrhages)	Some patients who took everolimus had bleeding problems.	Yes, by knowing: 1). All of the medicines the patient is taking, and 2). Any bleeding or bruising while taking everolimus.
Blood clots (Thrombotic and embolic events)	Some patients who took everolimus had blood clots in the lungs or blood clots in the legs. Sometimes people with cancer have an increased chance of having a blood clot.	Yes, by knowing what type of activity and how much activity to have each day.

Risk	What is known	Preventability
Irregular menstrual periods, including stopping of menstrual periods in women of child bearing age (Female fertility (including secondary amenorrhea))	Some women who took everolimus had menstrual cycles that were not at regular times or had no menstrual period at all.	Yes, by monitoring if menstrual periods are regular, not regular, or if there are no menstrual periods.
Infection you already have before you took everolimus that returns or worsens while you are taking everolimus (Pre-existing infection, (reactivation, aggravation, or exacerbation))	Everolimus may lower your body's ability to fight an infection. Some patients who had hepatitis B (a liver infection caused by a virus) before taking everolimus, had their hepatitis B infection reappear when they took everolimus. Some of the infections were severe (leading to respiratory or liver failure), and in a few patients, lead to death.	Yes, by: 1). Knowing about any infection in the past, 2). Knowing about any current infection and making sure the infection is fully gone before starting everolimus. 3). Reporting any signs and symptoms of an infection (such as fever) right away while taking everolimus.
Safety in patients with liver problems (Safety in patients with hepatic impairment)	Patients with liver problems may need to use a lower dose of everolimus.	Yes, by: 1). Knowing about any liver problems in the past, 2). Checking blood tests to look for liver problems before starting everolimus and while taking everolimus.

Table 5-2 Important potential risks

Risk	What is known
Development problems in young children taking everolimus (Postnatal developmental toxicity)	Juvenile male rats had their eyes open late and testes come out late and juvenile female rats had their eyes and vagina open late, which did catch up after stopping everolimus. Some juvenile rats took a longer time to remember and learn.
Pregnant or breast-feeding women	Pregnancy: Problems were seen in animal babies whose parent was given everolimus. It is not known if everolimus causes problems in human babies. Women of child bearing age should use birth control while taking everolimus and for up to 8 weeks after ending treatment with everolimus. Talk with your doctor about your birth control method to make sure it will be effective. Breast feeding: Everolimus was found in the breast milk of female rats. It is not known if everolimus goes into the breast milk of human women who take everolimus. Women taking everolimus should not breast feed.
Male infertility	In male rats who were given everolimus, fertility was reduced due to lower sperm count and lower sperm activity. The male rat sperm problem might not be permanent. It is not known if everolimus causes fertility problems in human men.

Risk	What is known
Muscle wasting / muscle loss	Everolimus can stop certain types of muscle cells from forming or growing. Your doctor will check your body weight.
CYP3A4: an enzyme in the body involved in drug metabolism (Interaction with strong CYP3A4 inhibitors and PgP inhibitors)	Some drugs may raise the blood level of everolimus. If you take everolimus with a drug like ritonavir or clarithromycin, your doctor may need to adjust your dose of everolimus.
CYP3A4: an enzyme in the body involved in drug metabolism (Interactions with moderate CYP3A4 inhibitors and PgP inhibitors)	Some drugs may raise the blood level of everolimus. If you take everolimus with a drug like erythromycin, your doctor may need to adjust your dose of everolimus.
CYP3A4: an enzyme in the body involved in drug metabolism (Interactions with strong CYP3A4 inducers and PgP inducers)	Some drugs may lower the blood level of everolimus. If you take everolimus with a drug like prednisone, your doctor may need to adjust your dose of everolimus.
CYP3A4: an enzyme in the body involved in drug metabolism (Interactions with CYP3A4 substrates and Pgp substrates)	Some drugs may cause the amount of everolimus in your blood to increase. Your doctor may need to adjust the dose of the other drug or the dose of everolimus.
Exemestane: another drug that is given with everolimus in some breast cancer patients (everolimus with concomitant exemestane use) (oncology only)	A few breast cancer patients had higher liver enzymes when they took everolimus with another drug called exemestane. But, a lot of these patients also had their cancer spread to their liver before taking the two drugs together.
ACE inhibitors: drugs that might be involved in the pharmacodynamics of angioedema onset (increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors)	Some drugs called ACE inhibitors may raise the risk of angioedema when taken with everolimus together.

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Table 5-3 Missing information

Topic	What is known
Giving everolimus to pediatric and adolescent patients for an unapproved use (off-label use in pediatric and adolescent patients)	Everolimus is not recommended for use in pediatric cancer patients. Everolimus is not recommended for patients under 18 years of age with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and liver function problems. Everolimus is not recommended for use in pediatric patients with TSC who have renal angiomyolipoma and no SEGA.
Patients with heart problems that might have become worse (patients with uncontrolled cardiac disease) (oncology setting)	It is not known if everolimus might worsen heart failure.
Long-term safety	Patients may need to take everolimus for a long time. Studies are being performed to get more information when patients take everolimus for a long period of time.
Possible cancer causing agent (onset of benign or malignant tumors)	Mice and rats were given a dose of everolimus that was similar to the human dose of 10 mg per day. The mice and rats were given this dose for up to 2 years. They did not develop tumors.
Changes to how the brain may grow and develop, and in those children younger than 3 years old (effects of everolimus on brain growth and development, particularly in patients under 3 years of age) (TSC only)	Little information is known about the development of the brain while being treated with everolimus, especially in patients younger than 3 years old.
Changes to how children can reason, remember, be attentive, speak; or changes in puberty, gender identity, future sexual behavior (neurocognitive and sexual development in pediatric patients) (TSC only)	Very little is known about a child's neurocognitive development or sexual development while being treated with everolimus.
Any difference when breast cancer patients take everolimus compared to when they take everolimus with exemestane (comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy) (oncology only)	Almost no information is known about the differences between when breast cancer patients take everolimus compared to when they take everolimus with exemestane.

Topic	What is known
Giving cytotoxic drugs like chemotherapy right before giving everolimus (safety in breast cancer patients pre-treated with cytotoxic therapies) (oncology only)	Little information is known about when breast cancer patients take drugs for their cancer (an example is cytotoxic chemotherapy) right before taking everolimus.

6 Summary of additional risk minimization measures by safety concern

There are no additional risk minimization activities for any of the safety concerns.

7 Planned post-authorization development plan

7.1.1 List of studies in post-authorization development plan

Table 7-1 List of studies in post-authorization development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Clinical study / CRAD001M2304	The primary objective is compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3 to 7 ng/mL and 9 to 15 ng/mL) vs. placebo in patients with TSC who are taking one to three AEDs.	Long-term safety Neurocognitive and sexual development in pediatric patients (TSC setting only)	Ongoing	Final CSR: 2Q2018
Clinical study / CRAD001M2305	The primary objective is to monitor the growth and development of pediatric patients with TSC associated SEGA previously enrolled in CRAD001M2301, who had received everolimus as part of study CRAD001M2301 and may or may not be continuing treatment with everolimus.	Postnatal developmental toxicity Long-term safety (TSC-SEGA setting only) Neurocognitive and sexual development in pediatric patients (TSC setting only)	Ongoing	Final CSR for PASS: 2026

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Disease registry / CRAD001MIC03	To map the course of TSC manifestations and their prognostic role; to identify patients with rare symptoms and co-morbidities; to record interventions and their outcomes; to contribute to create an evidence base for disease assessment and therapy and to inform further promote research in TSC; to measure quality of life in TSC patients; to collect information on sexual maturation/endo-crine assessments in patients with TSC, if available.	Male infertility Long-term safety (TSC setting only) Neurocognitive and sexual development in pediatric patients (TSC setting only)	Ongoing	Submission of annual interim analyses are planned yearly until study end. Final CSR for disease registry: 2Q2018 Final CSR for PASS: Dec-2027
Clinical study / CRAD001J2301	The primary objective of the study is to compare progression free survival (PFS) between combination treatment of everolimus/ trastuzumab/ paclitaxel and the combination treatment trastuzumab /paclitaxel in patients with HER2-overexpressing, unresectable locally advanced or metastatic breast cancer.	Long-term safety (Oncology setting only)	Ongoing	Final close-out CSR planned submission: 4Q2016. Additionally, this planned submission package will include comprehensi ve report providing exposure-response relationship data / information for PFS and OS: combining CRAD001J2 301 data with CRAD001W2 301 data.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Clinical study / CRAD001W2301	The primary objective is to compare the combination of everolimus, vinorelbine and trastuzumab to vinorelbine and trastuzumab alone with respect to progression-free survival in women with HER2/neu overexpressing locally advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.	Long-term safety (Oncology setting only)	Ongoing	Final close-out CSR planned submission: 4Q2016. Additionally, this planned submission package will include comprehensive report providing exposure-response relationship data / information for PFS and OS: combining CRAD001J2301 data with CRAD001W2301 data.
Clinical study / CRAD001Y2201	The primary objective is to estimate the hazard ratio of PFS for everolimus plus exemestane versus everolimus alone in postmenopausal women with ER positive, HER2 negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.	Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy Long-term safety (Oncology setting only)	Ongoing	Final PFS CSR planned submission: 1Q2018

7.1.2 Studies which are a condition of the marketing authorization

CRAD001C2485, CRAD001M2301, and CRAD001M2302 were studies that fell under specific obligations to complete post-authorization measures for the conditional marketing authorization of Afinitor / Votubia as everolimus in the TSC setting.

7.2 Summary of changes to the Risk Management Plan over time

Table 7-2 Major changes to the Risk Management Plan over time

RMP Version	RMP Date	Safety Concerns	Comment
2.3	10-Jun-2009	**Identified risks** Non-infectious pneumonitis Severe infections Hypersensitivity (anaphylactic reactions) Stomatitis Increased creatinine Hyperglycaemia / new onset diabetes **Potential risks** Cardiac failure Wound healing complications Lymphopenia Hypophosphataemia Dyslipidaemia Interactions with strong CYP3A4 and PgP inhibitors Interactions with moderate CYP3A4 and PgP inhibitors Interactions with CYP3A4 inducers and PgP inducers Interactions with CYP3A4 and PgP substrates **Missing information** Pediatric patients Pregnant or lactating women Hormonal contraceptives Patients with renal impairment Patients with severe hepatic impairment Patients with pre-existing infections (other than systemic invasive fungal infections) Patients with CNS metastases Patients with HIV or hepatitis B or C seropositivity Patients with bleeding diathesis Patients with coagulation disorders Patients with severe cardiac disease Patients with impairment of gastrointestinal function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Patients who have undergone surgery within 2 weeks prior to start of treatment Long-term safety Race other than Caucasian	
3	12-Apr-2010	Reactivation of background diseases (other than reactivation of hepatitis); added as important **missing information**.	
4	21-Oct-2010	Renal failure / proteinuria added as a **potential risk**.	
5	18-May-2011	Reclassified Wound healing complications, Dyslipidemia, Hypophosphatemia, Increased creatinine / proteinuria / renal failure, Hemorrhages, Thromboembolism to **identified risks**.	

RMP Version	RMP Date	Safety Concerns	Comment
		New identified **potential safety risks** of Developmental toxicity and Reproductive (teratogenicity) toxicity; and added Off-label use in pediatric and adolescent patients.	
6 / 4	14-Nov-2011	New **potential risks** of Intestinal obstruction / ileus, Infertility, and Secondary amenorrhea and removed risks (Severe infections, Hypersensitivity / anaphylactic reactions, Stomatitis, Wound healing complications, metabolic disorders (Hyperlipidemia, Hypophosphatemia, etc.) and Lymphopenia).	This RMP now combines both Afinitor and Votubia. This was Version 6 for Afinitor and Version 4 for Votubia
7 / 5	18-May-2012	Pre-existing infection, Pancreatitis, and Cholelithiasis have been added as **identified risks**.	
8 / 6	16-Nov-2012	Renamed **potential risk** to Pregnant or breast-feeding women. Update **DDI**. By-patient discussion of pediatrics younger than 3 years presenting Severe infections or Pre-existing infections AEs.	
9 / 7	16-May-2013	**Potential risk** of Reproductive (teratogenicity) toxicity was renamed as Pregnant or breast-feeding women.	New sections included and populated as required by the new template (issued, Jan 2013)
9 / 8	14-Nov-2013	Safety concern on new **missing information** item: effects of everolimus on brain growth and development, particularly in patients under 3 years of age.	The dataset for everolimus as Votubia in the TSC-SEGA setting only was updated in this version
9.1 / 8.1	09-Feb-2014	Safety concern on new **missing information** item: Postnatal development toxicity Pregnant or breast-feeding women Following safety concerns have been removed: Pediatric patients less than 3 years old Patients undergoing chronic treatment with steroids or another immunosuppressive agent.	
10 / 9	27-May-2014	Addition of **identified interaction**: Increased risk of angioedema when combining mTOR inhibitors with ACE inhibitors.	

RMP Version	RMP Date	Safety Concerns	Comment
		reintroduction of **missing information** topics: Comparative safety of everolimus combination, exemestane, vs. everolimus monotherapy; and new inclusion of Safety in breast cancer patients pretreated with cytotoxic therapies.	
11 / 10	19-May-2015	Previously existing **potential risk** of Male infertility also added as pharmacological class effect. Novartis fulfills three RMP commitments: CRAD001C2485, CRAD001M2301, CRAD001Y2301.	Major update
12 / 10	27-Jul-2015	Potential new population newly introduced with proposed indication for review.	Major update
11 / 11	18-Aug-2015	Novartis fulfills two additional RMP commitments in TSC setting: CRAD001M2302, pooled amenorrhea analysis. Female fertility (including secondary amenorrhea) in TSC setting was assessed.	Major update: Final extension-phase CSR of CRAD001M2302
12 / 11	14-Mar-2016	No change.	Minor administrative update: Approved Version 11.0 changes consolidated with Version 12.0 under review
12.1 / 11	25-Apr-2016	No change.	Minor administrative update: Alignment of proposed GI/Lung NET indication.
12.0 / 12.0	16-May-2016	Potential new population newly introduced with proposed indication for review. Included removal of Intestinal obstruction / ileus, Pancreatitis, Cholelithiasis; changed Cardiac failure (including ejection fraction decreased): per EMA's endorsement.	Major update
12.1/12.1	07-Oct-2016	Retained original name of the important identified risk Cardiac failure; updated elements of summary: per EMA's endorsement.	Minor update: Response to CHMP RSI / consolidation of approved Version 12.1 with Version 12.0 under review.
13.0 / 13.0	16-Feb-2017	Proposed revised dates for CRAD001MIC03 and CRAD001Y2201; updated elements of summary, per EMA's endorsement; removal / alignment of three Missing Information topics: per PRAC.	Minor update

This summary relates to EU RMP version 13.0/13.0 (data cut-off 31 Mar 2015) and was prepared in May 2018.