NOVARTIS

Regulatory Affairs

Everolimus – RAD001

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Everolimus*
Product(s) concerned (brand name(s)):	*Afinitor® and Votubia®*
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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 minimise 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 / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Afinitor®” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Afinitor®”.

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Summary of the risk management plan for Afinitor® (everolimus)

This is a summary of the risk management plan (RMP) for Afinitor and Votubia. The RMP details important risks of Votubia, how these risks can be minimized, and how more information will be obtained. There are no important identified risks, important potential risks and missing information for Afinitor.

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 or changes to the current ones will be included in updates of Afinitor and Votubia's RMP.

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 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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Afinitor and Votubia, together with measures to minimize such risks and the proposed studies for learning more about Afinitor and Votubia's risks are outlined below.

Measures to minimize the risks identified for medicinal products can be:

• Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

• Important advice on the medicine's packaging;

• The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

• The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Afinitor and Votubia is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Afinitor and Votubia are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Afinitor and Votubia. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine); There are no important identified/potential risks for Afinitor. A list of safety concerns for Votubia is presented in table 1.

Table 1 List of important risks and missing information	
Important identified risks	• Female infertility (TSC setting only)
Important potential risks	• Postnatal developmental toxicity (TSC setting only) • Male infertility (TSC setting only)
Missing information	• Long-term safety (TSC setting only) • Neurocognitive and sexual development in pediatric patients (TSC setting only)
There are no important identified/potential risks for Afinitor.	

II B: Summary of important risks

Table 2 Important identified risk: Female infertility (TSC setting only)	
Evidence for linking the risk to the medicine	The risk difference between Double-blind Everolimus and placebo/active comparator was 12.6% in the pooled TSC datasets. The review of the clinical database and safety database produced similar results. The analyses conducted in female patients with TSC who were aged 10 to 55 years, confirm that menstrual disorders, namely secondary amenorrhea and irregular menstruation are the main AEs seen while on treatment with everolimus. Most, if not all of these events, resolve while still on treatment with everolimus and without requiring intervention. There is no evidence of a delay in menarche among young female patients who were treated with everolimus. The preclinical data (pre-implantation loss, atrophic changes in uterus) and the clinical data evidence of everolimus treatment in association with menstrual disorders, including secondary amenorrhea and

	irregular menstruation, suggests that everolimus could impair female infertility. However, to date, there is no direct clinical evidence to suggest an effect of everolimus on hormonal imbalance or female infertility. Of note, all patients are required to take highly effective contraception while under treatment with everolimus and for at least eight weeks after stopping treatment. The terms of female infertility disorders are categorized as ADRs in TSC setting with appropriate frequency.
Risk factors and risk groups	Female patients of developmental or reproductive age receiving everolimus.
Risk minimization measures	**Routine risk minimization measures** Fertility in SmPC Section 4.6 Listed in SmPC Section 4.8. **Additional risk minimization measures** Not deemed necessary

Table 3 Important potential risk: postnatal developmental toxicity (TSC setting only)	
Evidence for linking the risk to the medicine	The risk difference between Double-blind Everolimus and placebo/active comparator was 0.6% in the pooled TSC datasets. There were no SAEs, only non-serious AEs. The AEs reported also included terms suggestive of female infertility disorders and are included as ADRs. **Non-clinical setting** In neonates and juvenile rats, everolimus caused systemic toxicity at systemic exposure below the therapeutic level. This was manifested as reduced body weight gains, reduced food consumption, and delayed developmental features (e.g. delayed eye opening, delayed reproductive development in both males and females) that were at least partially reversed after dosing cessation. 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 dosed up to 0.5 mg/kg for 4 weeks, everolimus treatment did not cause relevant toxicity. A pre- and post-natal

	development study in rats revealed slight body weight differences with survival of the F1 at ≥ 0.1 mg/kg. (Afinitor / Votubia EU-RMP V13.0 / V13.0-Section 13.1) **TSC population** Although no information has been identified specifically for SEGA, ANGIO, and TSC-Seizures patients, neurodevelopmental disorders are common in TSC. Developmental delay or learning difficulties were reported for 80% of 300 cases of TSC surveyed by postal questionnaire and reported by Hunt (1993) Joinson et al (2003) . in a study of 108 individuals with TSC found 44% with an IQ <70.
Risk factors and risk groups	Male and female patients of developmental age receiving everolimus (Yanchar et al 1996).
Risk minimization measures	**Routine risk minimization measures** Preclinical safety data in SmPC section 5.3 Breast-feeding in Package Leaflet Information for the Patients **Additional risk minimization measures** None
Additional pharmacovigilance activities	Stated additional PV activity for TSC-SEGA setting only: Study CRAD001M2305.

Table 4 Important potential risk: male infertility (TSC setting)	
Evidence for linking the risk to the medicine	The risk difference between Double-blind Everolimus and placebo/active comparator was 2.5% in the pooled TSC datasets. **Non-clinical setting** Reversible testicular tubular degeneration, reduced sperm count in epididymides; or, testicular morphology, sperm motility, sperm head count, and plasma testosterone levels were impacted in multiple animal species. Reproductive toxicology studies were conducted in rats and rabbits. In fertility studies in rats, everolimus caused testicular morphology change and a decrease in male fertility (with evidence of reversibility) but had no effect on female fertility.
Risk factors and risk groups	Male and female patients who are receiving everolimus and attempting to conceive a child.
Risk minimization measures	**Routine risk minimization measures**

	Contraception in SmPC Section 4.6 Fertility in SmPC Section 4.6. Preclinical safety data in SmPC Section 5.3. **Additional risk minimization measures** None

Table 5 Missing information: Long-term safety (TSC setting only)	
Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Stated additional PV activity for Long-term safety in TSC setting only: Study CRAD001M2305.

Table 6 Missing information: Neurocognitive and sexual development in pediatric patients (TSC setting only)	
Risk minimization measures	**Routine risk minimization measures** Section 4.2 of the SmPC **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Stated additional PV activity for Neurocognitive and sexual development in pediatric patients in TSC setting: CRAD001M2305.

II C: Post-authorization development plan

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

Table 7 Studies which are conditions of the marketing authorization	
Study short name	**Purpose of the 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.

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

Table 8 Other studies in the post-authorization development plan	
Study	**Rationale and study objectives**
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.