1 Part VI: Summary of the risk management plan (RMP) (Everolimus Sandoz, 2.5 mg, 5 mg and 10 mg, Tablets)

This is a summary of the RMP for everolimus 2.5 mg, 5 mg and 10 mg tablets. The RMP details important risks of everolimus tablets, how these risks can be minimized, and how more information will be obtained about everolimus tablets' risks and uncertainties (missing information).

Everolimus tablets' summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how everolimus should be used.

Important new concerns or changes to the current ones will be included in updates of theeverolimus tablet RMP.

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

Everolimus tablets are an anticancer medicines containing the active substance everolimus. Everolimus reduces the blood supply to the tumour and slows down the growth and spread of cancer cells.

Everolimus is used to treat adult patients with:

- hormone receptor-positive advanced breast cancer in postmenopausal women, in whom other treatments (so called "non-steroidal aromatase inhibitors") no longer keep the disease under control. It is given together with a medicine called exemestane, a steroidal aromatase inhibitor, which is used for hormonal anticancer therapy.
- advanced tumours called neuroendocrine tumours that originate from the stomach, bowels, lung or pancreas. It is given if the tumours are inoperable and do not overproduce specific hormones or other related natural substances.
- advanced kidney cancer (advanced renal cell carcinoma), where other treatments (so-called "VEGF-targeted therapy") have not helped stop your disease.

It contains everolimus as the active substance and it is given orally, in the form of 2.5 mg, 5 mg and 10 mg, tablets.

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

Important risks of everolimus tablets, with measures to minimize such 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 PL and SmPC addressed to patients and HCPs;
- 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 Periodic Safety Update Report (PSUR) assessment (if available) 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 everolimus is not yet available, it is listed under 'missing information' below.

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

Important risks of everolimus tablets 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 everolimus. 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).

Table 7-1 List of important risks and missing information

Important identified risks	Non-infectious pneumonitis
	Severe infections
	Hypersensitivity (anaphylactic reactions)
	Stomatitis
	Wound healing complications
	Increased creatinine/proteinuria/renal failure
	Hyperglycemia/new onset diabetes mellitus
	Dyslipidemia
	Hypophosphatemia
	Cardiac failure
	Cytopenia
	Hemorrhages
	Thrombotic and embolic events
	Female fertility (including secondary amenorrhea)
	Pre-existing infection (reactivation, aggravation, or exacerbation)
	Safety in patients with hepatic impairment
	Interaction with strong CYP3A4 inhibitors and PgP inhibitors
	Interaction with moderate CYP3A4 inhibitors and PgP inhibitors
	Interaction with strong CYP3A4 inducers and PgP inducers
	Interaction with CYP3A4 substrates and PgP substrates

	Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors
Important potential risks	Postnatal developmental toxicity
	Pregnant or breast-feeding women
	Male infertility
	Muscle-wasting/muscle-loss
	Interaction between everolimus and concomitant exemestane use
Missing information	Off-label use in pediatric and adolescent patients
	Long-term safety
	Onset of benign or malignant tumors
	Patients with uncontrolled cardiac disease
	Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy
	Safety in breast cancer patients pre-treated with cytotoxic therapies

7.2.2 Part VI – II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the originator product.

7.2.3 Part VI – II.C: Post-authorization development plan

7.2.3.1 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 everolimus tablets.

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

There are no studies required for everolimus tablets.