**Summary of risk management plan for Everolimus 2.5, 5 and 10 mg tablets (everolimus).**

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

Everolimus 2.5, 5 and 10 mg tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Everolimus 2.5, 5 and 10 mg tablets should be used.

## I. The medicine and what it is used for

Everolimus 2.5, 5 and 10 mg tablets are authorised for treatment of

- hormone receptor-positive advanced breast cancer;
- neuroendocrine tumours of pancreatic origin;
- neuroendocrine tumours of gastrointestinal or lung origin;
- renal cell carcinoma.

It contains everolimus as the active substance and it is given by oral administration.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Everolimus 2.5, 5 and 10 mg tablets, together with measures to minimise such risks and the proposed studies for learning more about Everolimus 2.5, 5 and 10 mg tablets' risks, are outlined below.

Measures to minimise 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Everolimus 2.5, 5 and 10 mg tablets is not yet available, it is listed under 'missing information' below.

### *II.A List of important risks and missing information*

Important risks of Everolimus 2.5, 5 and 10 mg tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 2.5, 5 and 10 mg tablets. 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).

| List of important risks and missing information | |
|---|---|
| Important identified risks | *Cardiac failure* |
| | *Cytopenia* |
| | *Drug interaction* with ACE inhibitors and increased risk of angioedema |
| | *Drug interaction* with CYP3A4 substrates and PgP substrates |
| | *Drug interaction* with moderate CYP3A4 inhibitors and PgP inhibitor |
| | *Drug interaction* with strong CYP3A4 inducers or PgP inducers |
| | *Drug interaction* with strong CYP3A4 inhibitors and PgP inhibitors |
| | Dyslipidaemia |
| | Female fertility (including secondary amenorrhea) |
| | Haemorrhages |
| | *Hyperglycaemia*/new onset diabetes mellitus |
| | Hypersensitivity (anaphylactic reactions) |
| | *Hypophosphataemia* |
| | Increased creatinine / proteinuria / renal failure |
| | Non-infectious pneumonitis |
| | Pre-existing infection (reactivation, aggravation, or exacerbation) |
| | Safety in patients with hepatic impairment |
| | Severe infections |
| | *Stomatitis* |
| | Thrombotic and embolic events |
| | Wound healing complications |
| Important potential risks | *Drug interaction* with exemestane |
| | Male infertility |
| | Muscle-wasting / muscle-loss |
| | Postnatal developmental toxicity |

| List of important risks and missing information | |
|---|---|
| | Pregnant or breast-feeding women |
| Missing information | Comparative safety of everolimus and exemestane therapy *versus* everolimus monotherapy |
| | Long-term safety |
| | *Off-label use* in paediatric and adolescent patients |
| | Onset of benign or malignant tumours |
| | Patients with uncontrolled cardiac diseases |
| | Safety in breast cancer patients pre-treated with cytotoxic therapies |

***II.B Summary of important risks***

The safety information in the proposed Product Information is aligned to the reference medicinal product Afinitor® (everolimus, Novartis Europharm Ltd).

***II.C Post-authorisation development plan***

**II.C.1 Studies which are conditions of the marketing authorisation**

There are no studies which are conditions of the marketing authorisation or specific obligation of the applicant's Everolimus 2.5, 5 and 10 mg tablets.

**II.C.2 Other studies in post-authorisation development plan**

There are no studies required for the applicant's Everolimus 2.5, 5 and 10 mg tablets.