VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Everolimus is used to treat the following cancers:

- breast cancer that is advanced (has started to spread) in women who have been through their menopause. Everolimus is used in breast cancer that is 'hormone receptor-positive' (when the cancer cells have oestrogen receptors on their surface) and 'HER2/neu negative' (when the cancer cells do not contain high levels of the HER2/neu [human epidermal growth factor receptor-2] protein). It is used together with a medicine called exemestane after other treatments called 'non-steroidal aromatase inhibitors' have failed;
- pancreatic neuroendocrine tumours (tumours of the hormone-producing cells in the pancreas) when the cancer cells are well- or moderately differentiated (which means that they have a similar appearance to normal pancreas cells) and the cancer is getting worse. It is used when the cancer is metastatic (has spread to other parts of the body) or when it cannot be surgically removed;
- neuroendocrine tumours (NET) of gastrointestinal or lung origin are a rare kind of cancer. NET start from neuroendocrine cells inside any organ called the stomach, lung, small intestine, appendix, colon, or pancreas. NET can release a substance called a hormone, so they can also be called functional or not functional. About half of patients with NET from the gastrointestinal tract or lung live for 5 years after knowing they have this tumuor.
- advanced renal cell carcinoma (a type of kidney cancer), when the cancer has worsened despite treatment with a 'VEGF-targeted' medicine (a type of medicine that blocks the effects of vascular endothelial growth factor proteins).

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, everolimus represents an effective drug in the treatment of breast cancer, pancreatic neuroendocrine tumours, neuroendocrine tumours of gastrointestinal or lung origin, and advanced renal cell carcinoma.

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, everolimus can be considered effective in the proposed indications.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inflammation of the lungs not caused by an infection (Non-infectious pneumonitis)	Fever, coughing, difficulty breathing, wheezing (signs of inflammation of the lung, also known as pneumonitis) have been reported in patients taking everolimus.	Everolimus will only be prescribed by a doctor with experience in cancer treatment. Patients should follow all the doctor's instructions carefully.
Severe infections	Everolimus may weaken patient's immune system. Therefore, patients may be at risk of getting an infection while taking everolimus. Increased temperature and chills (signs of infection) have been reported in patients taking everolimus.	Patients should talk to their doctor before taking everolimus if they have an infection. It may be necessary to treat infection before starting everolimus therapy.
Severe allergic reactions (Hypersensitivity (anaphylactic reactions))	Patients should stop taking everolimus and seek medical help immediately if they experience any of the following signs of an allergic reaction: • difficulty breathing or swallowing, • swelling of the face, lips, tongue or throat, • and severe itching of the skin, with a red rash or raised bumps. Rash, itching, hives, difficulty breathing or swallowing, dizziness (signs of serious allergic reaction, also known as hypersensitivity) have been reported. Swelling of the face, around the eyes, mouth, and inside the mouth and/or throat, as well as the tongue and difficulty breathing or swallowing (also known as angioedema), may be signs of an allergic reaction.	Patients should not take everolimus if allergic to everolimus, to related substances such as sirolimus or temsirolimus, or to any of the other ingredients of this medicine. If thinking they may be allergic, patients should ask doctor for advice.
Mouth sores (Stomatitis)	Mouth sores associated with everolimus use have been reported.	Everolimus should only be prescribed by a doctor with experience in cancer treatment. Patients should follow all the doctor's instructions carefully.

Risk	What is known	Preventability
CYP3A4: an enzyme in the body involved in drug metabolism (Interaction with CYP3A4 substrates and PgP substrates)	Everolimus may affect the way some other medicines work. If patients are taking other medicines at the same time as everolimus, their doctor may need to change the dose of everolimus or the other medicines.	Patients are advised to tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.
ACE inhibitors: drugs that might be involved in the pharmacodynamics of angioedema onset (Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors)	Angiotensin-converting enzyme (ACE) inhibitors (such as ramipril) used to treat high blood pressure or other cardiovascular problems may increase the risk of side effects with everolimus.	Patients are advised to tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

IMPORTANT POTENTIAL RISKS

Risk	What is known (Including reason why it is considered a potential risk)
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: Everolimus could harm an unborn baby and is NOT recommended during pregnancy. Patients are advised to tell the doctor if they are pregnant or think that they may be pregnant. The doctor will discuss with patients whether they should take this medicine during the pregnancy. Women who could potentially become pregnant should use highly effective contraception during treatment. If, despite these measures, they think they may have become pregnant, should ask their doctor for advice before taking everolimus anymore. Breast-feeding: Everolimus could harm a breast-fed baby. Patients should NOT breast-feed during treatment. Patients are advised to tell their doctor if they are breast-feeding.
Blockage in intestines (Intestinal obstruction / ileus)	Patients treated with everolimus may be at an increased risk of developing this safety concern.

Risk	What is known (Including reason why it is considered a potential risk)
Male infertility	Everolimus may affect male fertility. Patients are advised to talk to their doctor if they wish to father a child.
Inflammation of the gland pancreas (Pancreatitis)	Patients treated with everolimus may be at an increased risk of developing this safety concern.
Stones in gallbladder (Cholelithiasis)	Patients treated with everolimus may be at an increased risk of developing this safety concern.
Muscle-wasting / muscle-loss	Patients treated with everolimus may be at an increased risk of developing this safety concern.
Exemestane: another drug that is given with everolimus in some breast cancer patients (Everolimus with concomitant exemestane use)	Everolimus may affect blood levels of exemestane (hormonal anticancer therapy). No increase in side effects related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving these two medicines together. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

MISSING INFORMATION

Risk	What is known
Prescribing everolimus to paediatric and adolescent patients for an unapproved use (Off-label use in paediatric and adolescent patients)	Everolimus is not recommended for use in paediatric cancer patients.
Patients with kidney function problems (Patients with renal impairment)	Everolimus may impact patient's kidney function. Therefore, the doctor will monitor patient's kidney function while taking everolimus.
Patients with cancer that has spread to the brain (Patients with CNS metastases)	The safety and efficacy of everolimus in patients with CNS metastases (cancer spread to the brain) have not been established.
Patients with heart problems that might have become worse (Patients with uncontrolled cardiac disease)	It is not known if everolimus might worsen heart failure.
Patients who have stomach or intestine problems (Patients with impairment of GI function)	The safety and efficacy of everolimus in patients with impaired gastrointestinal function have not been established.
Long-term safety	The long term safety of everolimus has not been established.
Possible cancer causing agent (Onset of benign or malignant tumours)	Onset of benign or malignant tumours has not been established with everolimus use.

Risk	What is known
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)	Almost no information is known about the differences between when breast cancer patients take everolimus only compared to when they take everolimus with exemestane.
Giving cytotoxic drugs like chemotherapy right before giving everolimus (Safety in breast cancer patients pre-treated with cytotoxic therapies	Little information is known about when breast cancer patients take drugs for their cancer (an example is cytotoxic chemotherapy) right before taking everolimus.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable for pre-approval versions.