Everolimus (Afinitor®)

What it does and how it is used

- Everolimus (Afinitor, also available as Zoetress™ to prevent kidney transplant rejection) is indicated for the treatment of advanced renal cell carcinoma (RCC), subependymal giant-cell astrocytoma (SEGA) associated with tuberous sclerosis and progressive neuroendocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic.
- Everolimus and temsirolimus (Torisel) are part of a new class of therapies that block a special targeted protein known as the mammalian target of rapamycin or mTOR. These drugs exert their action by binding to intracellular proteins to form an inhibitory complex which leads to reduction of protein synthesis, inhibition of hypoxia-inducible factor (HIF-1) and reduced expression of vascular endothelial growth factor (VEGF). Blocking these pathways help reduce the growth, division and metabolism of cancer cells. Everolimus is taken daily by mouth whereas temsirolimus is given as an intravenous infusion once a week.
- **Renal cell carcinoma (RCC)** is the most common form of kidney cancer representing approximately 90% of cases.
- RCC is a cancer that affects the cells lining the small tubes of the nephrons. Nephrons are small filtering units that help produce urine in the kidney. In the early stages, there are rarely signs and symptoms, but later stages may present with flank pain, blood in the urine (hematuria), weight loss, fatigue, and a palpable abdominal mass. Many cases are discovered from incidental findings of a renal mass during radiographic examination.
- The median age of diagnosis is 65 years. A slight male predominance exists with a ratio of 1.6:1 for males vs. females.
- Some risk factors include smoking, obesity and hypertension. A few people have a rare, inherited disorder called Von Hippel-Lindau disease, an autosomal dominant, familial cancer syndrome, which causes some individuals to be more likely to develop several types of tumors, including renal cell carcinoma.
- Treatment of RCC is dependent on tumor type and disease stage. Treatment of metastatic or advanced RCC often involves the use of multiple kinase inhibitors such as sunitinib or sorafenib, which inhibit cancer cell growth by blocking angiogenesis (the formation of new blood vessels) in tumors.
- **Progression free survival (PFS)** is used as one predictor of clinical benefit in cancer clinical trials. Everolimus has been shown to significantly prolong PFS when compared to placebo (4 months vs. 1.9 months respectively). At 6 months, 26% of everolimus patients compared to 2% of placebo patients did not have progression of their RCC.
- Everolimus is indicated for use in advanced renal cell carcinoma after patients have tried and failed treatment with sorafenib (Nexavar) or sunitinib (Sutent).
- Other first-line therapies include bevacizumab (Avastin) plus interferon, pazopanib (Votrient), high dose interleukin-2, and temsirolimus (Torisel).
- **Subependymal giant-cell astrocytomas (SEGA)** are slow-growing, glioneuronal tumors that develop in 5 to 20% of patients with the tuberous sclerosis. Tuberous sclerosis is characterized by benign tumors in multiple organ systems including the brain, skin, kidney, lung, heart, and retina.
- SEGAs do not regress spontaneously and the volume increases progressively once serial growth is shown.
- Standard treatment for SEGAs is neurosurgical resection; however the location of these tumors can make resection difficult.
- SEGAs are associated with significant risk of illness and death, including sudden death from acute hydrocephalus. A reduction in volume by 30% or more is generally sufficient to reduce the risk of hydrocephalus or parenchymal invasion.
- Everolimus has been shown to significantly reduce the tumor volume. By 6 months, 75% of patients had tumor volume reduction of at least 30% (tumor volume was reduced by at least 30% in 21 out of 28 patients and 50% in 9 out of 28 of patients).
- Everolimus is indicated for use in patients with SEGAs associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection.
- **Neuroendocrine tumors** originate from cells throughout the nervous and endocrine systems which produce and secrete regulatory hormones. Common sites of origin include the pancreas; parathyroid, adrenal, and pituitary glands; calcitonin-producing cells of the thyroid; and argentaffin cells of the gut.
- Neuroendocrine tumors can be broadly categorized as those with (functional) and those without (nonfunctional) clinical syndrome. Most are slow-growing and malignant with metastasis to the lymph nodes and the liver or less commonly to bone, lung, brain, and other organs.
- The management of neuroendocrine tumors with surgical, medical, or radiation therapies depends on the specific endocrine gland(s) involved, grade of differentiation, aggressiveness and state of the tumor, amount of hormone produced, and specific patient needs.
Everolimus is listed as a treatment option for unresectable or metastatic neuroendocrine tumors by the National Comprehensive Cancer Network (NCCN).

Everolimus was studied in the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) Clinical Trial and when combined with the aromatase inhibitor exemestane, it improved progression-free survival in patients with hormone-receptor-positive advanced breast cancer that had been previously treated with nonsteroidal aromatase inhibitors.

The recommended dose of everolimus for RCC is 10 mg once daily. Any dose increase or reduction (for example, due to drug interactions) should be done in 5 mg increments (up to a max of 20 mg per day) and may be recommended based on individual safety and tolerability.

For SEGA, the initial dose is based on body surface area (BSA) with subsequent titration to achieve trough concentrations of 5-10 ng/mL. For example, a person with average BSA between 1.3 to 2.1 m² would require an initial dose of 5 mg once daily; if greater than or equal to 2.2 m² then 7.5mg once daily. Routine everolimus whole blood therapeutic drug concentration monitoring is recommended in SEGA.

A dose of 10 mg per day, with or without octreotide, was shown to be effective in patients with neuroendocrine tumors that are refractory to other chemotherapy.

It is recommended to increase the dose if everolimus is given concurrently with strong CYP3A4 inducers which are known to increase the clearance of everolimus. In hepatic insufficiency or cases of intolerance the dose of everolimus may be reduced to 5 mg a day.

Everolimus is currently being investigated for the treatment of various other forms of cancer including lymphoma, breast, gastric, and lung.

### What it costs

<table>
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<tr>
<th>Strength</th>
<th>AWP per tablet</th>
<th>AWP per month</th>
<th>AWP per year</th>
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<td>10 mg (1 tab) per day</td>
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### Rationale for prior authorization

To limit coverage of Afinitor to indications where it has been proven effective. For example, to provide coverage for the treatment of renal cell carcinoma in situations where there has been disease progression following use of sorafenib or sunitinib.

### Benefit design

- Coverage for Afinitor is determined through prior authorization for every claim.
- Coverage is provided for a quantity of tablets sufficient to treat renal cell carcinoma, subependymal giant cell astrocytoma (SEGA), or neuroendocrine tumors.

### Prior authorization criteria

1. Treatment of:
   - Advanced renal cell carcinoma in situations where there has been failure (disease progression) with sorafenib (Nexavar) or sunitinib (Sutent)
   - Subependymal giant cell astrocytoma (SEGA) in patients with tuberous sclerosis who are not eligible for curative surgical resection
   - Advanced, unresectable neuroendocrine tumors
   - Advanced estrogen-receptor positive breast cancer in postmenopausal women
     - in situations where the patient’s disease was refractory to letrozole (Femara) or anastrozole (Arimidex), AND
     - where everolimus will be used in combination with exemestane (Aromasin).
   - Advanced neuroendocrine tumors

2. Coverage is not provided for use in combination with sorafenib (Nexavar) or sunitinib (Sutent).
Coverage duration:
Breast cancer: 6 months. Coverage may be renewed in 6 month increments in situations where the patient continues to receive everolimus in combination with exemestane AND in the absence of disease progression.

Other indications: 12 months

Covered quantity (quantity per duration):
Coverage is provided for a quantity not to exceed 20 mg per day (up to sixty 10 mg tablets or thirty 2.5 mg, 5 mg or 7.5 mg tablets). Coverage for additional quantities is not provided.

References