Fact Sheet on Afinitor® in Advanced Renal Cell Carcinoma (RCC)

Afinitor is an oral drug approved for the treatment of advanced renal cell carcinoma in the European Union (EU) following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy. Afinitor inhibits the mTOR (mammalian target of rapamycin) pathway, which is responsible for multiple cellular functions including growth, metabolism and angiogenesis.

### About RCC
- Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for 80% to 85% of malignant kidney tumors. RCC develops in the lining of the kidney’s tubes and grows into a mass, or tumor.
- RCC accounts for approximately 4% of all new cancer cases worldwide. Annually, there are an estimated 330,000 new RCC cases and more than 100,000 deaths.
- More than one-third of patients with RCC have metastatic, or advanced, cancer at the time of diagnosis, meaning the cancer cells have spread to other parts of the body.

### The Advanced RCC Treatment Journey
A patient’s treatment journey will vary depending on the stage of the disease at diagnosis. Treatments for advanced RCC may include one or more of the following:
- Surgery: Removing all or part of the kidney (partial or full nephrectomy).
- First-line therapy: There are several therapies or combinations that may be considered after surgery to control or slow the growth of the tumor.
- Second-line therapy: Treatment that is given when initial therapy does not work or stops working.
- Third-line therapy: Treatment that is given when both first- and second-line therapies have failed to work or stops working.

Different medicines are appropriate for different patients, work in different ways, and have different side effects. There are many therapies available to treat advanced RCC and it is possible a patient may need multiple lines of therapy. Not every treatment option is available or approved for use in every stage.

### Afinitor in Advanced RCC
Afinitor is approved for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

Afinitor is an oral mTOR inhibitor approved for the treatment of advanced RCC.

### Mechanism of Action
Afinitor inhibits mTOR, a protein located inside cells responsible for regulating important signaling pathways. When overactivated, this can lead to uncontrolled cell growth, increased cellular metabolism and the creation of new blood vessels.

In in vivo/in vitro studies, inhibition of the mTOR pathway by Afinitor has been shown to:
- Reduce tumor cell growth and proliferation.
- Reduce cell metabolism.
- Decrease tumor angiogenesis.
Efficacy

In patients with advanced RCC whose disease has progressed on or after treatment with VEGF-targeted therapy:

- Afinitor more than doubled median time without tumor growth and reduced the risk of disease progression or death (progression-free survival) by 67% compared with placebo in the pivotal Phase III RECORD-1 trial, which formed the basis of global approvals for Afinitor.\(^{16}\)

Safety

- The most common adverse reactions (incidence ≥ 15%) from the RECORD-1 pivotal trial were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), diarrhea (30%), rash (29%), nausea (26%), anorexia (25%), peripheral edema (25%), dyspnea (24%), vomiting (20%), pyrexia (20%), mucosal inflammation (19%), headache (19%) and epistaxis (18%)\(^{16}\).

- The most common grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia\(^{16}\).

*Treatment approvals vary by country. Please check approved treatments in your country.

About Afinitor (everolimus)

Afinitor\(^{®}\) (everolimus) is approved in more than 115 countries including the United States and European Union for advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy. It is also approved in more than 95 countries, including the United States and throughout the European Union, for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin.

Afinitor (everolimus) is approved in the European Union for the treatment of hormone receptor-positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a nonsteroidal aromatase inhibitor (NSAI). In the United States, Afinitor is approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative (advanced HR+/HER2-) breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

Everolimus is also available from Novartis for use in certain non-oncology patient populations under the brand names Afinitor\(^{®}\) or Votubia\(^{®}\), Certican\(^{®}\) and Zortress\(^{®}\) and is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Indications vary by country and not all indications are available in every country. The safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

Important Safety Information about everolimus tablets

Afinitor/Votubia can cause serious side effects including lung or breathing problems, infections (including sepsis), and kidney failure, which can lead to death. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors may be at an increased risk for angioedema. Mouth ulcers and mouth sores are common side effects. Afinitor/Votubia can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and triglyceride levels. Afinitor/Votubia may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of child-bearing potential while receiving Afinitor/Votubia and for up to eight weeks after ending treatment. Women taking Afinitor/Votubia should not breast feed. Fertility in women and men may be affected by treatment with Afinitor/Votubia.

The most common adverse drug reactions (incidence ≥10 percent) are mouth ulcers, skin rash, feeling tired or weak, diarrhea, absence of menstrual periods, infections (including upper respiratory tract infection, sore throat and runny nose, sinusitis, and pneumonia), nausea, decreased appetite, low level of red blood cells, high levels of cholesterol, abnormal taste, acne, irregular menstrual periods, inflammation of lung tissue, high level of blood sugar, weight loss, itching, swelling of extremities or other parts of the body, nose bleeds, and headache. The most common Grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers, absence of menstrual periods, low level of red blood cells, infections (including pneumonia), high level of blood sugar, feeling tired or weak, low white blood cells, inflammation of lung tissue, diarrhea, and spontaneous bleeding or bruising. Cases of hepatitis B reactivation, blood
clots in the lung or legs, and pneumocystis jirovecii pneumonia (PJP) have been reported. Abnormalities were observed in hematology and clinical chemistry laboratory tests.

References

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