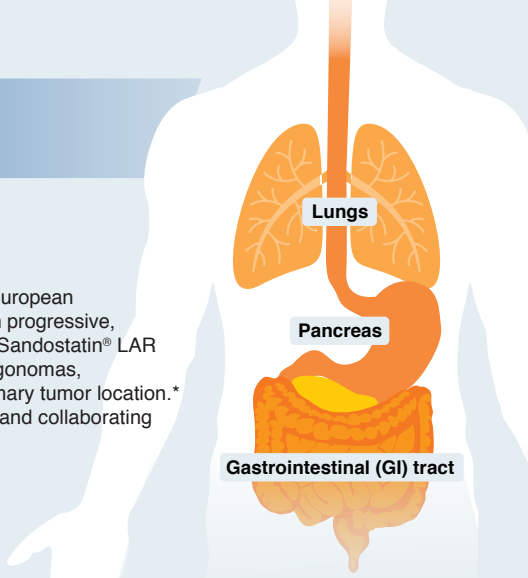
Novartis Heritage in Neuroendocrine Tumors (NET)

Neuroendocrine tumors, or NET, are malignant tumors that can occur throughout the body, including the gastrointestinal (GI) tract, lungs and pancreas



Novartis has a long heritage in the research, development and discovery of treatments for NET. Afinitor® is approved in more than 110 countries, including the US and in the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. Afinitor is also approved in the US and EU for the treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), nonfunctional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. Sandostatin® Injection and Sandostatin® LAR treat and provide symptom relief associated with functional gastro-entero-pancreatic (GEP-NET) carcinoid tumors with features of the carcinoid syndrome, VIPomas, glucagonomas, gastrinomas/Zollinger-Ellison syndrome, insulinomas and GRFomas. Sandostatin® LAR is also approved for the treatment of advanced NETs of the midgut or unknown primary tumor location.* Novartis supports the NET community by increasing disease awareness among healthcare professionals and the general public, improving patient services and education, and collaborating closely with researchers, patient groups, clinicians and professional societies.

HISTORY OF NET CLASSIFICATION, DIAGNOSIS AND MANAGEMENT

1888
NET first described

1907
The term "carcinoid" (karzinoide) first introduced to describe benign tumors of the gut

1929
Carcinoid reclassified to recognize the malignant potential of the tumors

1972
Neuron-Specific Enolase (NSE), an indicator of NET, first discovered

1982
Somatostatin receptors identified on neuroendocrine cells and tumors. The first somatostatin analogue, octreotide, is synthesized

1985
Synaptophysin, a neuroendocrine marker, first discovered

2000
World Health Organization (WHO) further classifies groups of NET by diagnostic factors

NOVARTIS HERITAGE AND DISCOVERY

1988
Food and Drug Administration (FDA) approves Sandostatin® (octreotide acetate) Injection for the treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors

1998
FDA approves Sandostatin® LAR Depot (octreotide acetate for injectable suspension) for the long-term treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors

2009
Phase III PROMID data published in the *Journal of Clinical Oncology* show Sandostatin LAR more than doubled the time to tumor progression vs. placebo (14.3 vs. 6 months) in patients with metastatic midgut NET. The most frequently observed serious adverse events (SAEs) affected the GI tract (Sandostatin LAR, n=6; placebo n=8), the hematopoietic system (Sandostatin LAR, n=5; placebo n=1) and general health status (fatigue and fever; Sandostatin LAR, n=8; placebo, n=2)*

2011
FDA and European Commission (EC) approve Afinitor tablets for adult patients with advanced NET of pancreatic origin
Phase III RADIANT-3 data published in the *New England Journal of Medicine* show that Afinitor more than doubled median progression-free survival from 4.6 months to 11 months compared to placebo in patients with advanced pancreatic NET. In the study, the most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhea and fatigue. The most common grade 3-4 adverse reactions (incidence ≥5%) were stomatitis, anemia and hyperglycemia**

2015
Phase III RADIANT-4 data published in *The Lancet* show that Afinitor increased median progression-free survival by 7.1 months in patients with nonfunctional, advanced, progressive GI and lung NET. In the pivotal trial, the most common adverse events (incidence ≥30%) were stomatitis, diarrhea and fatigue. The most common 3/4 adverse events (incidence ≥5%) were stomatitis, diarrhea and infections

2016
FDA and EC approve Afinitor tablets for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin in adults with progressive disease

...and beyond
Novartis remains committed to advancing the care and understanding of NET as well as to healthcare professional education and patient-oriented solutions

Please See Reverse for Important Safety Information
*Not all indications are approved in every country
**Lab abnormalities not shown

NOVARTIS ONCOLOGY

Novartis Pharma AG
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G-AFI-1139370

About Sandostatin® (octreotide acetate)

Sandostatin® Injection and Sandostatin® LAR are Indicated for:

The relief of symptoms associated with functional gastro-entero-pancreatic (GEP) neuroendocrine tumors: carcinoid tumors with features of the carcinoid syndrome, VIPomas, glucagonomas, gastrinomas/Zollinger-Ellison syndrome, insulinomas and GRFomas.

Sandostatin® LAR is also indicated for advanced neuroendocrine tumors of the midgut or unknown primary tumor location.

Contraindications

Known hypersensitivity to octreotide or to any of the excipients.

Warnings and Precautions

Patients should be carefully monitored for tumor expansion. Treatment could potentially restore fertility in female patients of child bearing potential. Use adequate contraception during treatment. Cases of bradycardia have been reported. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary. Gallbladder abnormalities may occur. Patients should be monitored periodically.

Rare instances of sudden escape from symptomatic control in patients with GEP neuroendocrine tumors may occur in patients being treated with Sandostatin Injection with rapid recurrence of severe symptoms.

Hypoglycemia or hyperglycemia may occur. Blood glucose levels should be monitored when treatment is initiated or when the dose is altered especially in patients with Type 1 diabetes. Antidiabetic treatment should be adjusted accordingly. Caution in patients with insulinomas or diabetes mellitus. These patients should be monitored closely.

Octreotide may alter absorption of dietary fats in some patients. Monitoring of vitamin B12 levels is recommended in patients with a history of vitamin B12 deprivation. Thyroid function should be monitored in patients receiving prolonged treatment with octreotide.

Caution in females of child-bearing potential. Patients should be advised to use adequate contraception. Use in pregnant women only under compelling circumstances. Do not breast-feed during treatment.

Adverse Events

The most commonly reported adverse reactions in clinical trials were diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycemia and constipation. Other commonly reported adverse reactions were dizziness, localized pain, biliary sludge, thyroid dysfunction (e.g.,decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycemia. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. In very rare instances, acute pancreatitis has been reported within the first hours or days of treatment and resolved on withdrawal of the drug. Cholelithiasis- induced pancreatitis has been reported on long-term treatment. ECG changes have been observed especially in patients with underlying cardiac diseases.

Post-marketing adverse reactions include: anaphylaxis, allergy/hypersensitivity reactions, urticaria, acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice, arrhythmia, increased alkaline phosphatase levels, and increased gamma glutamyl transferase levels.

About Afinitor® (everolimus)

Afinitor® (everolimus) tablets is approved in more than 110 countries, including the US and in the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. Afinitor is not indicated for the treatment of patients with functional carcinoid tumors in the US. Afinitor is now approved in the US and European Union for the treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), nonfunctional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. It is also approved in more than 120 countries including the US and European Union for advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy (in the US, specifically following sunitinib and sorafenib).

Additionally, Afinitor is approved in more than 110 countries including the United States and European Union for advanced HR+/HER2- breast cancer in combination with exemestane, after prior endocrine therapy.

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 3/4 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.

Afinitor® Important Safety Information

Afinitor/Votubia can cause serious side effects including lung or breathing problems, infections (including sepsis), and kidney failure, which can lead to death. 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 infections (including sore throat and runny nose, upper respiratory tract infection, pneumonia, sinusitis, and urinary tract infection), mouth ulcers, skin rash, feeling tired, diarrhea, fever, vomiting, nausea, cough, decreased appetite, low level of red blood cells, headache, abnormal taste, absence of menstrual periods, acne, inflammation of lung tissue, irregular menstrual periods, swelling of extremities or other parts of the body, high level of blood sugar, feeling weak, itching, weight loss, high levels of cholesterol, and nose bleeds. The most common Grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers, infections (including pneumonia), low level of red blood cells, high level of blood sugar, feeling tired, absence of menstrual periods, diarrhea, low white blood cells, inflammation of lung tissue, feeling weak, fever, 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.

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