

FDA approves new indication for Novartis drug Afinitor® for progressive, nonfunctional GI and lung neuroendocrine tumors (NET)

Feb 26, 2016

- *In advanced progressive, nonfunctional NET, Afinitor is the first approved treatment for patients with lung NET and the first oral therapy for GI NET*
- *Approval helps fulfill unmet need as progressive, nonfunctional gastrointestinal and lung NET are rare cancers with poor prognoses, limited treatment options[1],[2]*
- *Afinitor is now approved in the US in the three most common types of advanced NET; regulatory filings for GI/lung indication are underway in countries worldwide[3]*

The digital press release with multimedia content can be accessed here:



Basel, February 26, 2016 - Novartis today announced that the United States Food and Drug Administration (FDA) approved Afinitor® (everolimus) tablets for the treatment of adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. Afinitor received a priority review designation providing a shortened review period for drugs that treat serious conditions and offer a significant improvement in safety or effectiveness.

"Afinitor is the first treatment approved for progressive, nonfunctional NET of lung origin, and one of very few options available for progressive, nonfunctional GI NET, representing a shift in the treatment paradigm for these cancers," said Bruno Strigini, President, Novartis Oncology. "We are proud of our Afinitor development program, which has translated to meaningful benefits for patients with several different cancers and rare diseases."

Neuroendocrine tumors are a rare type of cancer that originate in neuroendocrine cells throughout the body, and are most often found in the GI tract, lungs or pancreas[1],[4]. NET can be defined as functional or nonfunctional. Functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances. Nonfunctional NET may be characterized by symptoms caused by tumor growth, such as intestinal obstruction, pain and

bleeding for GI NET, and asthma, chronic obstructive pulmonary disease and pneumonia for lung NET[5],[6],[7],[8]. More than 70% of patients with NET have nonfunctional tumors[9]. At the time of diagnosis, 5%-44% (depending on site of tumor origin) of patients with NET in the GI tract and 28% of patients with lung NET have advanced disease, meaning the cancer has spread to other areas of the body, making it difficult to treat[1],[4]. Progression, or the continued growth or spread of the tumor, is typically associated with poor outcomes[10].

The approval of Afinitor was based on efficacy and safety data from a pivotal study (RADIANT-4) showing Afinitor reduced the risk of progression in patients with progressive, well-differentiated, nonfunctional NET of GI or lung origin by 52% (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.35-0.67; $p < 0.001$) vs placebo. Additionally, the data showed Afinitor increased median progression-free survival (PFS) by 7.1 months: median PFS by central review was 11.0 months (95% CI, 9.2-13.3) in the Afinitor arm and 3.9 months (95% CI, 3.6-7.4) in the placebo arm[3].

In the pivotal trial, the most common treatment-related grade 3/4 adverse events (AEs) ($\geq 5\%$) for Afinitor and placebo, respectively, were infections (11.0% vs 2.0%), diarrhea (9.0% vs 2.0%), stomatitis (9.0% vs 0.0%), fatigue (5.0% vs 1.0%) and hyperglycemia (5.0% vs 0.0%)[3].

Additional worldwide regulatory filings for this indication are underway, with a decision in the EU anticipated in 2016.

RADIANT-4 Study: Part of the largest clinical trial program in advanced NET

RADIANT-4 (RAD001 In Advanced Neuroendocrine Tumors) is a Phase III prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter study. It examined the efficacy and safety of Afinitor plus best supportive care (BSC) vs placebo plus BSC in 302 patients with unresectable, progressive, well-differentiated, nonfunctional, locally advanced or metastatic NET of GI (excluding pancreatic) or lung origin. The major efficacy outcome measure of RADIANT-4 was PFS based on independent radiological assessment evaluated by Response Evaluation Criteria in Solid Tumors. Additional efficacy outcome measures were overall survival and best overall response rate (defined as complete response plus partial response)[3].

Patients were randomized 2:1 to receive daily Afinitor 10 mg or daily placebo orally. All patients received BSC during treatment, which excluded somatostatin analogues (SSAs). Patients had low or intermediate grade histology, no history or active symptoms of carcinoid syndrome, had documented disease progression within the previous 6 months and were required to have ceased treatment with SSAs for 4 weeks before study entry[3],[11].

The safety profile of Afinitor was consistent with what has been observed in previous studies of this drug. The most common treatment-related, all-grade AEs (incidence $\geq 30\%$) were stomatitis (63%), infections (58%), diarrhea (41%), peripheral edema (39%), fatigue (37%) and rash (30%). Afinitor was discontinued for adverse reactions in 29% of patients and dose reduction or delay was required in 70% of Afinitor-treated patients[3].

About Afinitor[®] (everolimus) tablets

Afinitor[®] (everolimus) tablets is now approved by the United States (US) Food and Drug

Administration (FDA) for the treatment of adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. Additionally, Afinitor is approved in 99 countries, including the US and throughout the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. It is also approved in >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).

Afinitor is also approved in 102 countries including the US 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 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 Afinitor[®] (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, infections (including upper respiratory tract infection, sore throat and runny nose, sinusitis, middle ear infection and pneumonia), absence of menstrual periods, high levels of cholesterol, nausea, decreased appetite, low level of red blood cells, acne, abnormal taste, irregular menstrual periods, inflammation of lung tissue, swelling of extremities or other parts of the body, high level of blood sugar, itching, weight loss, nose bleeds, cough and headache. The most common grade 3-4 adverse drug reactions (incidence ≥ 2 percent) are mouth ulcers, infections (including pneumonia), low level of red blood cells, absence of menstrual periods, high level of blood sugar, feeling tired or weak, diarrhea, low white blood cells, inflammation of lung tissue 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.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "underway," "anticipated," "yet," "will," "committed," "can," "may," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Afinitor (everolimus), or regarding potential future revenues from Afinitor. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Afinitor will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Afinitor will be commercially successful in the future. In particular, management's expectations regarding Afinitor could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected safety issues; unexpected manufacturing or quality issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 119,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit <http://www.novartis.com>.

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartis> ([link is external](#)).

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