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Novartis drug Afinitor® approved by FDA as first medication for children and adults with a benign brain tumor associated with tuberous sclerosis

- *Subependymal giant cell astrocytoma (SEGA) is a benign brain tumor associated with tuberous sclerosis (TS)*[1]
- *Prior to the approval of Afinitor, brain surgery was the only treatment option for patients with growing SEGAs*[1]
- *Approval is based on a 28-patient study showing nearly one-third of patients had a reduction of 50% or greater in the size of their largest SEGA at six months*[2]
- *Worldwide regulatory submissions underway, including applications filed in the EU and Switzerland*

East Hanover, N.J., October 29, 2010 — Novartis Pharmaceuticals Corporation ("Novartis") announced today that the US Food and Drug Administration (FDA) has approved Afinitor® (everolimus) tablets for patients with subependymal giant cell astrocytoma (SEGA), a benign brain tumor associated with tuberous sclerosis (TS), who require therapeutic intervention but are not candidates for curative surgical resection[2].

This accelerated approval of Afinitor is based on an open-label, single-arm, 28-patient study conducted by Cincinnati Children's Hospital Medical Center[2]. The effectiveness of Afinitor is based on an analysis of change in SEGA volume. A Phase III study is underway that compares Afinitor to placebo to explore the clinical benefits of Afinitor for the treatment of patients with SEGA associated with TS[3].

Prior to this FDA approval, the only treatment option for growing SEGAs, which primarily affect children and adolescents, was brain surgery[1,4,5]. Tuberous sclerosis is a genetic disorder affecting approximately 25,000 to 40,000 people in the US that may cause benign tumors to form in vital organs[6]. SEGAs, benign brain tumors, occur in up to 20% of patients with TS[1].

"Today's FDA decision is an important milestone for the children and adults living with SEGA associated with tuberous sclerosis," said Hervé Hoppenot, President of Novartis Oncology. "We are committed to furthering research for patients with tuberous sclerosis and will continue to work towards addressing their unmet medical needs."

In this study, nearly one-third of patients (32%) experienced a reduction of 50% or greater in the size of their largest SEGA at six months relative to baseline. None of the patients developed a new SEGA while receiving Afinitor[2].

The most common adverse reactions observed (incidence ≥30%) in the open-label, single-arm trial were mouth sores, upper respiratory tract infections, sinusitis, middle ear infections and fever[2].

“SEGAs can be challenging for individuals with tuberous sclerosis and for the whole family, which is why we are encouraged to see ongoing research and new treatment options like Afinitor for these individuals,” said Vicky Whittemore, Vice President and Chief Scientific Officer of the patient advocacy group the Tuberous Sclerosis Alliance.

For the treatment of patients with SEGA associated with TS, Afinitor received FDA priority review status, which is granted to drugs that offer major advances in treatment. This indication was approved under the FDA’s accelerated approval program, which provides patients access to a treatment where previously there was an unmet medical need even though clinical benefit has yet to be confirmed[7]. Novartis is continuing to study the efficacy and clinical benefit of Afinitor for patients with SEGA associated with TS in a Phase III trial[3].

Novartis has submitted marketing applications for everolimus to the European Medicines Agency (EMA) and the Swiss Agency for Therapeutic Products (Swissmedic), and additional regulatory submissions are underway worldwide.

About the study

In an open-label, single-arm study, 28 patients aged three years and above (median age=11, range 3-34) with evidence of SEGA growth initially received everolimus orally at a dose of 3 mg/m^2. As of March 8, 2010, the median duration of treatment was 24.4 months (range 4.7-37.3 months)[2].

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The reliability of the frequency of adverse reactions and laboratory abnormalities reported in this trial is limited because of the small number of patients. The most common adverse reactions (≥10%, all grades) reported among the 28 patients with evidence of established SEGA growth included: stomatitis or mouth sores (86%), upper respiratory tract infection (82%), sinusitis (39%), middle ear infection (36%), fever (32%), convulsion (29%), acne-like skin inflammation (25%), diarrhea (25%), cellulitis or acute infection of the deep tissues of skin or muscle (21%), vomiting (21%), cough (21%), body tinea or fungal infection (18%), headache (18%), personality change (18%), rash (18%), skin infection (18%), dry skin (18%), gastroenteritis or inflammation of the gastrointestinal tract (18%), contact dermatitis (14%), dizziness (14%), external ear infection (14%), allergic rhinitis or inflammation of nasal passages (14%), gastric infection (14%), nasal congestion (14%), excoriation or skin abrasion (14%), acne (11%), constipation (11%), abdominal pain (11%) and pharyngitis or inflammation of the pharynx (11%)[2].

Grade three adverse reactions included convulsion, infections (single cases of sinusitis, pneumonia, tooth infection and viral bronchitis) and single cases of stomatitis, aspiration, cyclic neutropenia, sleep apnea syndrome, vomiting, dizziness, white blood cell count decreased and neutrophil count decreased. A grade four convulsion was reported[2].

Key laboratory abnormalities observed in >1 patient (and listed in decreasing order of frequency) included elevations in aspartate transaminase (AST) concentrations (89%), total cholesterol (68%), alanine transaminase (ALT) concentrations (46%), triglycerides (43%) (hypertriglyceridemia reported as adverse reaction in 11% of patients, blood triglycerides increased reported as adverse reaction in 7% of patients), glucose (25%) and creatinine

(11%), and reductions in white blood cell counts (54%) (reported as adverse reaction in 11% of patients), hemoglobin (39%), glucose (32%) and platelet counts (21%). Most of these laboratory abnormalities were mild (grade one). Single cases of grade three elevated AST concentrations and low absolute neutrophil count (ANC) were reported. No grade four laboratory abnormalities were noted. Two cases of neutrophil count decreased and blood immunoglobulin G decreased were reported as adverse reactions[2].

All data from the study reported in this press release are based on the cut-off date of March 8, 2010.

About the EXIST-1 Phase III trial
EXIST-1, a Phase III randomized, placebo-controlled trial aimed at evaluating the results of the open-label, single-arm trial, is examining everolimus treatment in patients with SEGAs associated with TS. Endpoints include SEGA response, seizure rate and skin lesion response rate. The trial has completed accrual and patients continue to be followed[3].

The trial involves patients in 10 countries, including Australia, Belgium, Canada, Germany, Italy, the Netherlands, Poland, Russia, the UK and the US[3].

About Afinitor (everolimus)
Afinitor® (everolimus) tablets is now approved in the US to treat patients with SEGA associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of Afinitor is based on an analysis of change in SEGA volume. Improvement in disease-related symptoms or increase in survival has not been shown. Afinitor is available in the US in 2.5 mg, 5 mg and 10 mg tablet strengths.

For more information visit www.AFINITOR.com/SEGA-TS or call 1-888-4-AFINITOR. US patients who may be eligible for financial assistance can learn about the AfiniTRAC™ reimbursement support program by contacting 1-888-9-AfiniTRAC or visiting the Afinitor website.

Afinitor is also approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib and in the European Union (EU) for the treatment of patients with advanced RCC whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

In the US, everolimus is available in different dosage strengths under the trade name Zortress® for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. In the EU, everolimus is available in different dosage strengths under the trade name Certican® for the prevention of organ rejection in heart and kidney transplant recipients.

Not all indications are available in every country. As an investigational compound, the safety and efficacy profile of everolimus has not yet been established outside the US in patients with SEGA associated with TS. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for SEGAs anywhere else in the world.

Important Safety Information about Afinitor (everolimus) tablets
Patients should not take Afinitor if they are allergic to Afinitor or to any of its ingredients. Patients should tell their healthcare provider before taking Afinitor if they are allergic to sirolimus (Rapamune®) or temsirolimus (Torisel®).

Afinitor can cause serious side effects including infections or lung or breathing problems.

Afinitor may make patients more likely to develop an infection, such as pneumonia, or a bacterial, fungal or viral infection. Viral infections may include reactivation of hepatitis B in people who have had hepatitis B in the past. In some people these infections may be severe, and can even lead to death. Patients may need to be treated as soon as possible. Patients should tell their healthcare provider right away if they have a temperature of 100.5˚F or above, chills or do not feel well. Symptoms of hepatitis B or infection may include the following: fever, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, pale stool or dark urine, yellowing of the skin or pain in the patient's upper right side.

In some patients lung or breathing problems may be severe, and can even lead to death. Patients should tell their healthcare provider right away if they have any of these symptoms: new or worsening cough, shortness of breath, difficulty breathing or wheezing. Patients may need to stop taking Afinitor for a while or use a lower dose.

Afinitor can cause mouth ulcers and sores. Patients should tell their healthcare provider if they have pain, discomfort or open sores in their mouth. Their healthcare provider may tell them to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.

Patients will have regular blood tests before they start and during their treatment with Afinitor. These tests will monitor how their kidneys and liver are working, their blood sugar and cholesterol levels as well as the number of blood cells in their body. Patients who receive Afinitor for the treatment of SEGA will need regular blood tests to measure how much Afinitor is in their blood since this will help their doctor decide how much Afinitor they need to take.

Afinitor may affect the way other medicines work, and other medicines can affect how Afinitor works. Using Afinitor with other medicines can cause serious side effects. Patients should tell their healthcare provider about all of the medicines they take, including prescription and non-prescription medicines, vitamins, herbal supplements such as: St. John's Wort, and medicine for fungal infections, bacterial infections, tuberculosis, seizures, HIV-AIDS, heart conditions or high blood pressure and medicines that suppress their immune system. Patients should not drink grapefruit juice or eat grapefruit during their treatment.

Patients should not take Afinitor tablets which are broken or crushed. Patients should not chew or crush the tablets.

Patients should tell their healthcare provider about all their medical conditions, including if they have or have had liver problems, diabetes or high blood sugar, high cholesterol levels, infections, hepatitis B or other medical conditions.

Patients should tell their healthcare provider if they are scheduled to receive any vaccinations. Patients should not receive a live vaccine or be around people who have recently received a live vaccine during treatment with Afinitor.

It is not known if Afinitor will harm a patient's unborn baby. Patients should use effective birth control while using Afinitor and for 8 weeks after stopping treatment.

Common side effects of Afinitor in patients with SEGA include mouth ulcers, infections of the respiratory tract, sinuses and ears and fever. Common side effects of Afinitor in patients with advanced kidney cancer include mouth ulcers, infections, feeling weak or tired, cough and diarrhea.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as “to explore,” “committed,” “will,” “can,” “encouraged,” or similar expressions, or by express or implied discussions regarding potential new indications or labeling for Afinitor or regarding potential future revenues from Afinitor. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Afinitor to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Afinitor will be submitted or approved for any additional indications or labeling in any market. Nor can there be any guarantee that Afinitor will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding Afinitor could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; the company’s ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. 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

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, the Novartis Group offers a diversified portfolio to best meet these needs: innovative medicines, preventive vaccines, diagnostic tools, cost-saving generic pharmaceuticals and consumer health products. The Novartis Group is the only company with leading positions in each of these areas. In 2009, the Group's continuing operations achieved net sales of USD 44.3 billion, while approximately USD 7.5 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 100,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.us.novartis.com.

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