

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG**Novartis drug Votubia[®] approved in the EU as first medication to treat patients with non-cancerous kidney tumors associated with TSC**

- *Prior to this approval, surgical intervention was the only option in Europe for these tuberous sclerosis complex (TSC) patients^{1,2}*
- *Kidney tumors, or renal angiomyolipomas, affect up to 80% of patients with TSC and growing tumors may lead to life-threatening complications^{1,3}*
- *Approval marks the second TSC-related indication for Votubia in the EU, where it is also approved to treat a non-cancerous brain tumor associated with TSC²*

Basel, November 5, 2012 – Novartis received approval from the European Commission (EC) for Votubia[®] (everolimus) tablets* for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery². This marks the first approval of a medical treatment in this patient population in Europe^{1,2}.

“Renal angiomyolipomas affect the vast majority of patients with TSC and over time can cause debilitating symptoms, a decline in renal function, and possibly even the need for kidney transplant or dialysis,” said Dr. Chris Kingswood, Royal Sussex County Hospital, Brighton, United Kingdom. “This approval represents a major advance in the treatment of the disease in Europe, giving clinicians a non-surgical option to manage TSC kidney tumors.”

This approval is based on data from the Phase III EXIST-2 (EXamining everolimus In a Study of TSC) trial, which found that 42% of patients taking everolimus experienced an angiomyolipoma response versus 0% of patients in the placebo arm ($p < 0.0001$). The evidence is based on analysis of the change in the sum of the angiomyolipoma volume. Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the everolimus arm ($p < 0.0001$)².

“For the first time, European patients living with renal angiomyolipoma associated with TSC now have an effective non-surgical option,” said Hervé Hoppenot, President, Novartis Oncology. “This approval reinforces the potential of Votubia to treat a wide range of manifestations associated with TSC, a debilitating, lifelong disease where there remains critical unmet need.”

Up to 80% of patients with TSC, a genetic disorder that may cause non-cancerous tumors to form in vital organs, develop renal angiomyolipomas. Typical onset occurs between the ages of 15 and 30 and prevalence increases with age³. Over time, these kidney tumors may grow large enough to cause severe internal bleeding, require emergency surgical interventions, such as embolization and nephrectomy, and lead to kidney failure or cardiovascular diseases^{1,3,4}. The tumors can be difficult to manage as

*Known as Afinitor[®] (everolimus) tablets for certain patients with SEGA and renal angiomyolipoma associated with TSC in the US and other countries.

they may be numerous and often form in both kidneys³. In the EU, approximately 7,000 TSC patients have large growing renal tumors (>3 cm) at risk of bleeding^{5,6,7}.

Everolimus works by inhibiting mTOR, a protein implicated in many tumor-causing pathways^{2,8}. TSC is caused by defects in the *TSC1* and/or *TSC2* genes². When these genes are defective, mTOR activity is increased and can cause uncontrolled tumor cell growth and proliferation, blood vessel growth and altered cellular metabolism^{8,9}. According to preclinical studies, by inhibiting mTOR activity in this signaling pathway, everolimus reduces cell proliferation and blood vessel growth⁸.

This EC approval follows a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) adopted for Votubia in September 2012 for the treatment of renal angiomyolipoma associated with TSC and applies to all 27 EU member states, plus Iceland and Norway.

About EXIST-2

EXIST-2 is the first double-blind, randomized, placebo-controlled, international, multicenter Phase III study for the treatment of patients with renal angiomyolipoma associated with TSC. Trial patients (median age=31, range 18-61) were randomized 2:1 to receive either everolimus (n=79) or placebo (n=39) at a daily dose of 10 mg. The median duration of blinded study treatment was 48 weeks in the everolimus arm and 45 weeks in the placebo arm².

In the study, 42% of patients on everolimus (33 of 79; 95% confidence interval [CI] 30.8-53.4) experienced an angiomyolipoma response versus 0% on placebo (0 of 39; 95% CI 0.0-9.0; p<0.0001), defined as a 50% or greater reduction in the sum of angiomyolipoma volume relative to baseline, the absence of new tumor growth at least 1 cm in longest diameter, absence of kidney volume increase of 20% or greater and no renal angiomyolipoma-related bleeding of Grade 2 or higher².

Everolimus demonstrated improvement when compared to placebo for both key secondary endpoints measured: time to angiomyolipoma progression and skin lesion response rate. There were three patients in the everolimus arm and eight patients in the placebo arm with documented angiomyolipoma progression by central radiologic review. The time to angiomyolipoma progression was longer in patients on everolimus (hazard ratio [HR] 0.08, 95% CI 0.02-0.37; p<0.0001). Skin lesion response rate was higher in the everolimus arm. A partial clinical response in skin lesions (corresponding to a 50% or greater improvement) was observed by Physician Global Assessment in 26% of patients on everolimus, compared with 0% of patients on placebo (p=0.0011). No complete responses were observed².

The most common adverse reactions reported in the everolimus arm during the double-blind period (with an incidence at least 15%) included stomatitis, hypercholesterolemia, aphthous stomatitis, mouth ulceration and acne. The most common Grade 3 adverse reactions in the everolimus arm (with an incidence of at least 2%) were amenorrhea, aphthous stomatitis and mouth ulceration. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia and anemia. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia².

About everolimus

Everolimus is now approved in the European Union (EU) as Votubia[®] (everolimus) tablets for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume. Everolimus is also approved in the United States (US) as Afinitor[®] (everolimus) tablets for the treatment of adult patients with renal

angiomyolipomas and TSC, who do not require immediate surgery. The effectiveness of Votubia in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

Everolimus is also approved in the EU as Votubia for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with TSC, who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated. In the US, everolimus is approved as Afinitor and Afinitor Disperz™ in pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC have not been demonstrated.

Everolimus is also available from Novartis as Afinitor for use in oncology settings and for use in other non-oncology patient populations under the brand names 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.

Important Safety Information about Votubia/Afinitor

Votubia/Afinitor can cause serious side effects including lung or breathing problems, infections and renal failure which can lead to death. Mouth ulcers and mouth sores are common side effects. Votubia/Afinitor can affect blood cell counts, kidney and liver function, and blood sugar and cholesterol levels. Votubia/Afinitor may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of child-bearing potential while receiving Afinitor and for up to 8 weeks after ending treatment. Women taking Votubia/Afinitor should not breast feed.

The most common adverse drug reactions (incidence $\geq 15\%$) are mouth ulcers, diarrhea, feeling weak or tired, skin problems (such as rash or acne), infections, nausea, swelling of extremities or other parts of the body, loss of appetite, headache, inflammation of lung tissue, abnormal taste, nose bleeds, inflammation of the lining of the digestive system, weight decreased and vomiting. The most common Grade 3-4 adverse drug reactions (incidence $\geq 2\%$) are mouth ulcers, feeling tired, low white blood cells (a type of blood cell that fights infection), diarrhea, infections, inflammation of lung tissue, diabetes and amenorrhea. Cases of hepatitis B reactivation and blood clot in the lung and leg have been reported.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as “potential,” or similar expressions, or by express or implied discussions regarding potential new indications or labeling for everolimus or regarding potential future revenues from everolimus. 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 everolimus to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that everolimus will be submitted or approved for any new indications or labeling in any market, or at any particular time. Nor can there be any guarantee that everolimus will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding everolimus could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected regulatory

actions or delays or government regulation generally; competition in general; government, industry and general public pricing pressures; unexpected manufacturing issues; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; 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

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, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2011, the Group's continuing operations achieved net sales of USD 58.6 billion, while approximately USD 9.6 billion (USD 9.2 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Novartis Group companies employ approximately 127,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit <http://www.novartis.com>.

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