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MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis drug Votubia® receives EU approval to treat refractory partial-onset seizures in patients with TSC

- *Votubia is the first adjunctive treatment approved in the EU specifically for partial-onset seizures in children and adults with tuberous sclerosis complex (TSC)*
- *Approval addresses unmet need as up to 60% of patients with TSC suffering from seizures become unresponsive to available anti-epileptic therapies*[1]
- *Decision marks the third TSC-related indication for Votubia in the EU, where it is also approved to treat SEGA and renal angiomyolipomas*[2]

Basel, January 31, 2017 – Novartis today announced that the European Commission has approved Votubia® (everolimus) dispersible tablets* as an adjunctive treatment for patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with tuberous sclerosis complex (TSC). Votubia is now the first approved pharmacologic therapy in all 28 member states of the European Union (EU), plus Iceland and Norway, specifically for the treatment of refractory partial-onset seizures associated with TSC[2].

"With this latest approval of Votubia in the EU, patients with TSC suffering from refractory partial-onset seizures – one of the most debilitating manifestations of TSC – now have a new therapeutic option to address a critical unmet need," said Bruno Strigini, CEO, Novartis Oncology. "This is a welcome advance and an important milestone in our ongoing commitment to improving care for this patient community."

The EU approval of Votubia was based on efficacy and safety data from a pivotal Phase III study (EXIST-3: EXamining everolimus In a Study of TSC), which found that when used as an adjunctive therapy, Votubia significantly reduced the frequency of refractory partial-onset seizures associated with TSC compared to placebo. Efficacy and safety of two trough exposure concentrations of Votubia, 3–7 ng/mL (low exposure) and 9–15 ng/mL (high exposure) were assessed. Patients in all treatment arms concomitantly received one to three anti-epileptic drugs (AEDs) during the eighteen weeks of study core phase. The youngest patient enrolled was two years of age. Seizure response rate (≥50% reduction) was significantly greater with Votubia low exposure (LE) (28.2%, 95% confidence interval [CI] 20.3 – 37.3; p=0.008) and high exposure (HE) (40.0%, 95% CI 31.5 – 49.0; p<0.001) vs placebo (15.1%, 95% CI 9.2 – 22.8). The median percentage reduction from baseline in seizure frequency was also significantly greater among patients randomized to Votubia LE (29.3%, 95% CI 18.8 – 41.9; p=0.003) and HE (39.6%, 95% CI 35.0 – 48.7; p<0.001) vs placebo (14.9%, 95% CI 0.1 – 21.7). The most common all-grade adverse events (AEs) of any cause reported during the core phase at frequencies ≥15% in Votubia LE/HE arms included stomatitis, diarrhea, nasopharyngitis, upper respiratory tract infection, and pyrexia[3].

Tuberous sclerosis complex is a rare genetic disorder affecting up to one million people worldwide[4]. Approximately 85% of individuals with TSC are affected by epilepsy, and uncontrolled seizures associated with TSC can be debilitating for patients[1]. Votubia is the only approved non-surgical option indicated for treating non-cancerous brain and kidney tumors in

certain patients with TSC. EXIST-3 is the first Phase III study to demonstrate the significant benefit of adjunctive Votubia in the treatment of refractory partial-onset seizures in patients with TSC[2,5]. These data may be used to support regulatory filings in other countries.

Votubia works by inhibiting the mammalian target of rapamycin (mTOR), a protein that regulates multiple cellular functions. TSC is caused by mutations in the *TSC1* or *TSC2* genes, resulting in hyperactive signaling of the mTOR pathway which can lead to increased cellular growth and proliferation, neuronal hyper-excitability, abnormalities in cortical architecture and network function and impaired synaptic plasticity[6,7]. Pre-clinical research suggests that hyperactive mTOR activity may influence several mechanisms of epileptogenesis, the gradual process by which the brain develops epilepsy in TSC[8].

About EXIST-3 (EXamining everolimus In a Study of TSC)
EXIST-3 is a Phase III, three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of high and low exposure ranges of Votubia as adjunctive therapy in patients with TSC who have refractory partial-onset seizures, defined as seizures persisting despite the use of two or more sequential regimens of single or combined anti-epileptic drugs (AEDs). The study enrolled male and female participants (ages 2.2 – 56.3 years) with clinically defined TSC, who were on stable doses of one to three AEDs for at least four weeks prior to a two-month, pre-randomization, evaluation period[2,3].

The primary objective was to assess the effectiveness of adjunctive Votubia as compared to placebo in reducing refractory partial-onset seizures in patients with TSC. Secondary objectives included the percentage of patients free from seizure during the maintenance period, change in seizure frequency, and safety.

The most frequent (≥10%) all grade adverse events (AEs), of any cause, reported with Votubia LE/HE vs placebo included stomatitis (54.7%/63.8% vs 9.2%), diarrhea (17.1%/21.5% vs 5.0%), nasopharyngitis (13.7%/16.2% vs 16.0%), upper respiratory tract infection (12.8%/15.4% vs 12.6%), pyrexia (fever) (19.7%/13.8% vs 5.0%), vomiting (12.0%/10.0% vs 9.2%), cough (11.1%/10.0% vs 3.4%), and rash (6.0%/10.0% vs 2.5%). Grade 3 or 4 AEs occurred in 13 (10.9%) patients in the placebo group, 21 (17.9%) patients in the LE group, and 31 (23.8%) patients in the HE group[3].

About tuberous sclerosis complex
Tuberous sclerosis complex (TSC) may cause non-cancerous tumors to form in vital organs including the brain, kidney, heart, lungs, and skin, as well as resulting disorders such as epilepsy, autism, cognitive impairment, behavioral problems, and psychiatric disorders. Many people with TSC show evidence of the disease in the first year of life. However, because manifestations vary from person to person and can take years to develop, many children are not diagnosed until later in life, often with the onset of seizures, skin lesions or other significant symptoms, such as developmental delays. Because TSC is a lifelong condition, the latest professional diagnostic guidelines issued in 2012 advise that individuals be monitored by a doctor experienced with the disorder to ensure tumor growth or new symptoms are identified early[6,9].

About Votubia (everolimus)
In the European Union (EU), everolimus is approved as Votubia tablets for the treatment of adult patients with renal angiomyolipoma associated with 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 in sum of angiomyolipoma volume. Votubia tablets and dispersible tablets are also indicated in the EU for the treatment of patients 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. Votubia dispersible tablets are also indicated in the EU as an adjunctive treatment for patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC.

In the United States (US), everolimus is approved as Afinitor® tablets for the treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery. Afinitor tablets and Afinitor Disperz™ (dispersible tablets) are also indicated in the US in pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected.

Additionally, Afinitor tablets are approved in >110 countries, including the US and EU, for the treatment of advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy (in the US, specifically following sunitinib and sorafenib); locally advanced, metastatic or unresectable progressive neuroendocrine tumors (NET) of pancreatic origin; and for advanced HR+/HER2- breast cancer in combination with exemestane, after prior endocrine therapy. It is also approved in >40 countries, including the US and EU, for the treatment of adult patients with progressive, well-differentiated (Grade 1 or 2), nonfunctional NET of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.

Everolimus is available from Novartis under the brand names Afinitor, Certican® and Zortress® for use in oncology and transplant patient populations 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
Votubia/Afinitor 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. Votubia/Afinitor can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and triglyceride levels. Votubia/Afinitor may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of child-bearing potential while receiving Votubia/Afinitor and for up to eight weeks after ending treatment. Women taking Votubia/Afinitor should not breast feed. Fertility in women and men may be affected by treatment with Votubia/Afinitor.

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.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “advance,” “milestone,” “ongoing,” “commitment,” “may,” “suggests,” “yet,” “will,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Votubia, or regarding potential future revenues from Votubia. 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 Votubia 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 Votubia will be commercially successful in the future. In particular, management’s expectations regarding Votubia could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; 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; safety, quality or manufacturing 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 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion (USD 8.4 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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

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