

## Everolimus Use in Children with Tuberous Sclerosis Complex

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Everolimus was initially approved by the Food and Drug Administration (FDA) in 2009 for the treatment of adults with advanced renal cell carcinoma. It has subsequently been approved for the treatment of neuroendocrine tumors of pancreatic origin, renal angiomyolipomas, and some forms of advanced breast cancer. It is also used off-label for immunosuppression after solid organ transplantation. Everolimus was approved in 2010 for the treatment of subependymal giant cell tumor (SGCT, also referred to as subependymal giant cell astrocytoma or SEGA) associated with tuberous sclerosis complex (TSC) in adults and children 3 years of age and older.<sup>1,2</sup> On August 29, 2012, the FDA announced an expanded approval to children 1 year of age and older, along with a new dispersible tablet formulation for smaller doses.<sup>3</sup> Over the past year, a number of significant papers have been published which add to our understanding of the role of everolimus in SGCT and suggest potential use in other manifestations of TSC in children.

### Mechanism of Action

Tuberous sclerosis complex is an autosomal dominant genetic disorder that results in the development of tumors in the brain, kidney, lungs, or skin.<sup>1,2</sup> It is estimated that 80% of patients with TSC have a mutation of one of the two tuberous sclerosis genes (TSC1 and TSC2). The TSC1 gene on chromosome 9q34 encodes the protein hamartin, while the TSC2 gene on chromosome 16p13 encodes the protein tuberin. Hamartin and tuberin form a heterodimer that is involved in regulating the function of mammalian target of rapamycin (mTOR). The mTOR pathway integrates cellular inputs involved in multiple downstream signaling cascades needed for cellular growth, proliferation, and metabolism. The hamartin/tuberin heterodimer inhibits activation of mTOR complex 1 (mTORC1), a serine-threonine kinase. Mutations in TSC1 or TSC2 result in an inability to form the hamartin/tuberin heterodimer, which leads to mTORC1 being upregulated and results in increased activity in

the downstream kinase signaling cascade. As a result, there is disruption of cell cycle progression, transcription, translation and metabolic control throughout the body. Patients with TSC may present with neurologic lesions (such as SGCT or cortical tubers), renal angiomyolipomas, pulmonary lymphangioleiomyomatosis, or cutaneous fibromas. Clinical manifestations may include seizures, neurocognitive impairment, or autism.

While SGCTs are slow-growing tumors, they have the potential to produce significant morbidity or sudden death from acute hydrocephalus. Surgical resection remains the primary means of managing SGCTs, but complete resection is not always achievable. Everolimus is a derivative of rapamycin that inhibits mTORC1 by binding to FKBP-12, an intracellular protein. This results in inhibition of the mTOR pathway and blockade of downstream kinase signaling cascade activation.<sup>1,2,4,5</sup> Everolimus has been shown to be effective in reducing the impact of hyperactive mTOR signaling in patients with SGCTs, as measured by reduced tumor growth, and may be effective in slowing the growth of renal angiomyolipomas, pulmonary lymphangioleiomyomatosis, and facial angiofibromas, as well as reducing the frequency of TSC-associated seizures.<sup>6,7</sup>

### Pharmacokinetics

Peak everolimus concentrations are achieved 1-2 hrs following administration of an oral dose. Administration with a high-fat meal results in a reduced systemic exposure to everolimus, with a reduction in the area under the concentration-time curve (AUC) of 16-22% and a reduction in peak whole blood concentrations of approximately 60%. Everolimus is 74% protein bound. It is metabolized by cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (PgP) and undergoes significant intestinal, or first-pass, metabolism. Six metabolites have been identified in humans, but appear to have little or no pharmacologic activity. The elimination half-life of everolimus is approximately 30 hrs in adults.<sup>1,2,4</sup>

### Clinical Experience

The efficacy of everolimus in treating SGCT and other TSC-related tumors has been evaluated in several clinical trials. An initial phase I/II open-label single-center trial was conducted in 28 patients with TSC (mean age 11 years, range 3-34 years).<sup>6</sup> Everolimus was initiated at a dose of 3 mg/m<sup>2</sup> given once daily, with subsequent adjustments to maintain whole blood concentrations of 5-15 ng/mL. The median dose at completion of the study was 5.6 mg/m<sup>2</sup> (range 1.5-10.5 mg/m<sup>2</sup>). All patients experienced improvement. After 6 months, the median reduction in the volume of the patient's largest lesion was 0.80 cm<sup>3</sup> (range 0.4-1.2 cm<sup>3</sup>,  $p < 0.001$ ). Twenty-one patients (75%) had a  $\geq 30\%$  reduction, with nine (32%) experiencing a  $\geq 50\%$  reduction. A reduction in tumor volume of 30% was considered by the authors to be enough to significantly reduce or eliminate the risk for hydrocephalus. No patients had evidence of new lesions, increased intracranial pressure, or worsening hydrocephalus. None required surgical intervention or other therapies. There was also a significant reduction in seizure frequency (median -1,  $p = 0.02$ ) and an improvement in the mean Quality of Life in Childhood questionnaire score ( $63.4 \pm 12.4$  at 3 months and  $62.1 \pm 14.2$  at 6 months, compared to a baseline score of  $58.7 \pm 14$ ). The authors also noted that among the 15 patients in the study who had facial angiofibromas, 13 experienced improvement.

At the conclusion of the study, patients could enroll in a 5-year extension phase.<sup>8</sup> The results of the first 3 years were published in the February 2013 issue of *Neurology*. Twenty-five patients were still receiving everolimus, with a mean daily dose of 5.3 mg/m<sup>2</sup> (range 2.1-12.3 mg/m<sup>2</sup>). At all assessments (18, 24, 30, and 36 months), at least 65% of patients had a reduction in tumor volume  $\geq 30\%$ . Twenty-four patients had completed 2 years of treatment, with a median reduction in SGCT volume of 0.71 cm<sup>3</sup> (range 0.24-9.03 cm<sup>3</sup>). Eleven patients had a reduction of  $\geq 50\%$ . Improvement was noted in eight of the nine patients with facial angiofibromas. Seizure frequency was also reduced at 2 years compared to baseline. In both papers, the most common adverse effects were stomatitis (in up to 79% of patients), pyrexia, and acne (each in 25%). There were no adverse effects requiring discontinuation. In a separate publication, the authors noted that three of the four patients who had surgical resection prior to enrollment continued to have a  $\geq 50\%$  reduction in tumor volume, and none experienced recurrent hydrocephalus.<sup>9</sup>

A phase III international randomized, double-blind, placebo-controlled trial of everolimus (EXIST-1) was conducted in 117 children and adults with SGCT associated with TSC.<sup>10</sup> The patients (median age 9.5 years, range 0.8-26

years) were treated with a starting dose of 4.5 mg/m<sup>2</sup> given once daily, with adjustment to maintain trough concentrations of 5-15 ng/mL. MRI scans were obtained at baseline, 12, 24, and 48 weeks. Twenty-seven of the 78 patients receiving everolimus demonstrated a  $\geq 50\%$  reduction in tumor volume versus none in the placebo group ( $p < 0.0001$ ). There was no progression in the everolimus group, while six of the placebo patients experienced SGCT enlargement ( $p = 0.0002$ ). No significant difference was seen in seizure frequency, which the authors suggested may have resulted from an inadequate number of assessments. Improvement in skin lesions was reported in 30 (42%) of the everolimus patients, compared to four (11%) of the controls ( $p = 0.0004$ ). The authors also evaluated improvement in the 44 patients with angiomyolipomas. Sixteen (53%) of the patients given everolimus improved, with no change in those given placebo.

Based on these findings, a second trial (EXIST-2) was conducted to better assess response to everolimus in adults with both angiomyolipoma and TSC or sporadic lymphangiomyomatosis.<sup>11</sup> Forty-two percent of the patients given everolimus demonstrated a  $\geq 50\%$  reduction in lesion volumes, with no change occurring in the controls ( $p < 0.0001$ ).

The efficacy of everolimus in reducing seizure frequency was evaluated in another open-label phase I/II study.<sup>12</sup> A total of 20 children (median age 8 years, range 2-21 years) with TSC were treated. In order to be included in the study, the children had to have medically refractory epilepsy, defined as having received at least two antiepileptics and having had at least eight seizures within the 30 days prior to enrollment. Everolimus was initiated at a dose of 5 mg/m<sup>2</sup>. The median daily treatment dose after 12 weeks was 8.4 mg/m<sup>2</sup>. The median reduction in seizure frequency was 73% ( $p < 0.001$ ), based on family-maintained seizure diaries. Twelve patients (60%) experienced a  $\geq 50\%$  reduction. Median seizure frequency during 23-hour EEG monitoring decreased from 3.5 to 1.5 ( $p = 0.007$ ). Only three patients had more frequent seizures after treatment. Parents also reported improved behavior in their children. Quality of Life for Children in Epilepsy questionnaire scores showed a significant improvement ( $p < 0.001$ ). The most common adverse effects were stomatitis or mucositis and upper respiratory tract infection (each in 90% of patients).

### Contraindications and Warnings

Everolimus can produce severe hypersensitivity reactions, including anaphylaxis and angioedema. Further treatment with everolimus or other rapamycin derivatives is considered contraindicated in patients experiencing these reactions. As with other rapamycin derivatives, everolimus has been associated with the

development of non-infectious pneumonitis. In clinical trials, this has been reported in 19% of patients, with 2-4% having severe disease (grade 3 or 4). Patients and their families should be aware of the need to contact their health care provider for signs of cough, dyspnea, or hypoxia. Everolimus may be continued at a reduced dose in patients with grade 1 or 2 pneumonitis, but should be discontinued in cases classified as grade 4 and held until resolution or significant improvement in grade 3 pneumonitis.<sup>4</sup>

#### Adverse Effects

Safety data on everolimus was gathered from the 117 adults and children in the EXIST-1 trial.<sup>10</sup> There were no cases of discontinuation resulting from adverse effects, but 55% of the patients receiving everolimus required at least one dose reduction or dosage adjustment. The most commonly reported adverse effects were stomatitis (in 62% of the everolimus group compared to 26% of controls), respiratory tract infections (31% and 23%), pyrexia (23% and 18%), vomiting (22% and 13%), anxiety or behavioral disturbance (21% and 3%), rash (21% and 8%), diarrhea (17% and 5%), and fatigue (14% and 3%). Constipation, gastroenteritis, pharyngitis, and acne were each reported in 10% of everolimus patients and in 5% or fewer controls. Amenorrhea was reported by three of the 18 females between 10 and 55 years of age and none of the females receiving placebo.

Laboratory abnormalities included an elevated partial thromboplastin time (72% of the everolimus group and 44% of the controls), neutropenia (46% and 41%), anemia (41% and 21%), an elevated aspartate transaminase (33% and 0), an elevated alanine transaminase (18% and 3%), hypercholesterolemia (81% and 39%), and hypertriglyceridemia (27% and 15%).

#### Drug Interactions

The metabolism of everolimus may be significantly altered by the concomitant use of CYP3A4 or Pgp inhibitors. The use of strong CYP3A4 inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinavir, telithromycin, ritonavir, or voriconazole should be avoided. The use of moderate CYP3A4 or Pgp inhibitors (amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, or verapamil) may be considered, but requires a reduction in the everolimus dose (see *Dosing Recommendations*). The use of strong CYP3A4 inducers (carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and rifapentine) with everolimus is not recommended. If no alternatives are available, the dose of everolimus should be doubled. In any patient requiring the use of an interacting drug, everolimus concentrations should be closely monitored throughout treatment.

Administration of everolimus with oral midazolam may produce an increase in the maximum midazolam concentration of 25%. Use of everolimus with depot octreotide may increase trough octreotide concentrations by 50%. Concomitant administration of everolimus with exemestane in patients with breast cancer may result in increased exemestane concentrations.

#### Availability

Everolimus is marketed by Novartis as both Afinitor® and Zortress®. Afinitor® is available in two dosage forms: standard tablets and dispersible tablets that are mixed with water to form an oral suspension. The standard tablets are available in 2.5 mg, 5 mg, 7.5 mg, and 10 mg strengths. The dispersible tablets (Afinitor Disperz®) are available in 2 mg, 3 mg, and 5 mg strengths. Both products are dispensed in cartons of four blister cards of seven tablets. Zortress® is indicated for immunosuppression following kidney or liver transplantation in adults and is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets.

#### Dosing Recommendations

The recommended dose of everolimus for the treatment of SGCT in patients with TSC is 4.5 mg/m<sup>2</sup> given orally once daily. Doses should be rounded to the nearest tablet strength. If the calculated dose is below the lowest tablet strength, the dose should be administered every other day. Combining both dosage forms (tablets and the dispersible tablets) for one patient is not recommended. The dose of everolimus should be reduced to 2.5 mg/m<sup>2</sup> daily for patients with severe hepatic impairment (Child-Pugh class C) or in patients on concomitant therapy with drugs that are moderate CYP3A4 or Pgp inhibitors. The dose should be increased to 9 mg/m<sup>2</sup> daily in patients requiring concomitant treatment with drugs that are strong CYP3A4 inducers.

Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be crushed. The dispersible tablets should be dissolved in water to create an oral suspension and given within 1 hour of preparation. The suspension can be made in an oral syringe by placing the tablet(s) in the syringe and adding 5 mL of water and 4 mL of air prior to replacing the syringe tip. The syringe should be gently inverted 5 times for adequate mixing. After the contents are given, the syringe should be filled with another 5 mL of water and the process repeated so that the entire dose is administered.

If using a drinking glass (or cup) for preparation, the tablet(s) should be placed into the glass with 25 mL of water. Doses greater than 10 mg should be prepared in two glasses. Allow 3 minutes for the tablet(s) to dissolve and then stir the liquid gently with a spoon just prior to administration. Add another 25 mL of water to the glass, stir, and administer to ensure that the

entire dose is given. If preparing an everolimus dose for another person, the individual preparing the dose should wear gloves to minimize contact with the drug. The dose should not be prepared by a woman who is pregnant or planning to become pregnant because of potential fetal risk.

Everolimus should be taken at the same time each day, consistently with food or consistently without food. If a dose is missed, it may be taken up to 6 hrs after the usual administration time. If more than 6 hrs have passed, the dose should be skipped and treatment resumed the next day. Patients should not eat foods or use dietary supplements that might inhibit CYP3A or Pgp activity, such as grapefruit juice, or induce these enzymes, such as St. John's wort. Patients taking everolimus should not receive live vaccines or be in close contact with someone who has received a live vaccine until the period for potential viral shedding is over.<sup>4</sup>

Everolimus doses should be titrated to maintain trough concentrations of 5-15 ng/mL. A trough should be obtained 2 weeks after the start of therapy, and again every 3 to 6 months in growing children and in patients with a recent change in body surface area, or every 6-12 months in adults with a stable body surface area. Patients with hepatic impairment should have a trough checked with any evidence of a change in hepatic function. A trough should also be checked 2 weeks after the initiation or discontinuation of a drug known to alter the metabolism of everolimus.<sup>4</sup>

If the everolimus concentration is < 5 ng/mL, the daily dose should be increased by one tablet (either one 2.5 mg tablet or one 2 mg dispersible tablet). For concentrations > 15 ng/mL, the daily dose should be decreased by one tablet. If the resulting dose is less than one tablet, the dose should be administered every other day. In patients with mild to moderate dose-related adverse effects, the dose should be reduced by 50%. Therapy should be held or discontinued for severe adverse reactions.<sup>4</sup>

### Summary

Everolimus has been found to be a valuable tool in the management of children with TSC. To date, studies have documented its efficacy in the treatment of SGCT, with significant reductions in tumor burden as well as seizure frequency. Preliminary studies suggest that everolimus may be of benefit in the renal angiomyolipomas and skin lesions seen with TSC as well. More research will be needed to fully define the role of everolimus in children and adults with TSC.

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### **Formulary Update**

The following actions by the Pharmacy and Therapeutics Committee at their January meeting:

1. Riociguat (Adempas<sup>®</sup>) was added to the Formulary for treatment of patients with pulmonary arterial hypertension or persistent or recurrent thromboembolic pulmonary hypertension.
2. Golimumab (Simponi<sup>®</sup>) was added for the treatment of ankylosing spondylitis, psoriatic arthritis, or ulcerative colitis and rheumatoid arthritis when used in conjunction with methotrexate.

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