Everolimus (Afinitor) Tablets

**Manufacturer:** Novartis Pharmaceuticals, East Hanover, N.J.

**Indication:** Everolimus is indicated for patients with advanced renal cell carcinoma after unsuccessful treatment with sunitinib (Sutent, Pfizer) or sorafenib (Nexavar, Bayer).

**Drug Class:** An antineoplastic agent, everolimus belongs to the class of drugs called kinase inhibitors, which thwart the growth of tumors by blocking cells’ ability to communicate. The molecular formula is C_{53}H_{83}NO_{14}, and the molecular weight is 958.2. This derivative of rapamycin works in a fashion similar to that of rapamycin as an inhibitor of the mammalian target of rapamycin (mTOR).

**Uniqueness of Drug:** Everolimus is an inhibitor of mTOR, a serine–threonine kinase, downstream from the PI3K/AKT pathway that is normally responsible for cellular process (e.g., cell growth, angiogenesis, and apoptosis). The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein (FKBP-12), resulting in an inhibitory complex formation and inhibition of mTOR kinase activity.

Everolimus reduces the activity of S6 ribosomal protein kinase and eukaryotic elongation factor 4E-binding protein, down-stream effectors of mTOR, involved in protein synthesis. The drug also inhibits the expression of hypoxia-inducible factor and reduces the expression of vascular endothelial growth factor. In *in vitro* and *in vivo* studies, inhibition of mTOR by everolimus reduced cell proliferation, angiogenesis, and glucose uptake.

**Warnings and Precautions:**

**Noninfectious pneumonitis.** Noninfectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. In a randomized study, noninfectious pneumonitis was reported in 14% of patients receiving everolimus. The incidence of grade 3 and 4 noninfectious pneumonitis, according to Common Toxicity Criteria (CTC), was 4% and 0%, respectively. Fatal outcomes have been observed. Noninfectious pneumonitis should be suspected in patients with nonspecific respiratory signs and symptoms (hypoxia, pleural effusion, cough, or dyspnea) and in whom infectious, neoplastic, and other causes have been excluded. Patients are advised to promptly report any new or worsening respiratory symptoms.

Patients with radiological changes suggesting noninfectious pneumonitis and with few or no symptoms may continue everolimus therapy without any dose alterations. If symptoms are moderate, therapy should be interrupted until symptoms improve, and the use of corticosteroids may be indicated. Everolimus may be reintroduced at a dose of 5 mg daily.

If symptoms are severe, everolimus therapy should be discontinued and corticosteroids may be indicated until clinical symptoms resolve. Everolimus may be restarted at a reduced dose of 5 mg daily, depending on individual circumstances.

**Infections.** Everolimus has immunosuppressive properties and may predispose patients to infections, especially opportunistic infections. Localized and systemic infections (e.g., pneumonia, bacterial infections, invasive fungal infections, aspergillosis, candidiasis) have occurred in patients taking everolimus. Some of these infections have been severe (leading to respiratory failure) or fatal. Physicians and patients should be aware of the increased risk of infection with everolimus. If signs or symptoms of infection develop, appropriate treatment should be instituted promptly. Pre-existing invasive fungal infections should be treated before patients begin taking everolimus. If an invasive systemic fungal infection occurs during therapy, everolimus should be discontinued and an antifungal drug given.

**Oral ulceration.** In the randomized study, approximately 44% of everolimus-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 or 2. In such cases, topical treatments are recommended, but mouthwashes containing alcohol or peroxide can exacerbate the condition and should be avoided. Antifungal agents should not be used unless a fungal infection has been diagnosed.

**Laboratory Tests and Monitoring:**

**Renal function.** Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen or serum creatinine, is recommended before patients begin everolimus therapy and periodically thereafter.

**Blood glucose and lipids.** Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in trials. Monitoring of fasting serum glucose and lipid profile is recommended before everolimus therapy begins and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before patients begin taking everolimus.

**Hematological parameters.** Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported. Monitoring the complete blood count is recommended before therapy starts and should be conducted periodically thereafter.

**Drug–drug interactions.** Because of significant increases in exposure of everolimus, patients should avoid taking it along with strong or moderate inhibitors of cytochrome P450 3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, ritonavir, ampeprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, or diltiazem) or P-glycoprotein at the same time. An increase in the everolimus dose is recommended when it is given together with a strong CYP 3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, or phenobarbital).

**Hepatic impairment.** The safety and pharmacokinetic properties of everolimus were evaluated in a study involving

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eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment; therefore, a dose reduction is recommended. Everolimus has not been studied in patients with severe hepatic impairment (Child-Pugh class C), and it should not be used in this population.

**Vaccinations.** During treatment with everolimus, patients should not receive live vaccines and should not be in close contact with those who have received live vaccines, such as intranasal influenza, measles–mumps–rubella, oral polio, and bacille Calmette-Guérin, yellow fever, varicella, and TY21a typhoid vaccines.

**Use in pregnancy.** Everolimus is a Pregnancy Category D drug. Although no adequate or well-controlled studies of everolimus in pregnancy have been conducted, everolimus may cause fetal harm when administered to pregnant women. Everolimus caused embryofetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if a woman becomes pregnant while taking the drug, she should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to use an effective method of contraception while using everolimus and for up to eight weeks after ending treatment.

**Dosage and Administration:**

**Recommended dosage:** For patients with advanced renal cell carcinoma, everolimus 10 mg is taken once daily at the same time every day, either with or without food. The tablets should be swallowed whole with a glass of water; they should not be chewed or crushed. Treatment should continue for as long as clinical benefits are observed or until unacceptable toxicity occurs.

**Dose modifications.** If severe or intolerable adverse reactions occur, a temporary dose reduction or an interruption of everolimus therapy may be required. If the dose needs to be reduced, the suggested dose is 5 mg daily.

**Hepatic impairment:** For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C), and it should not be used in this patient population.

**Strong CYP 3A4 inducers:** The use of concomitant strong CYP 3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, and phenobarbital) should be avoided. If patients require coadministration of a strong CYP 3A4 inducer, increasing the everolimus dose from 10 mg daily up to 20 mg daily in 5-mg increments can be considered. This dose is predicted to adjust the area-under-the-curve (AUC) concentration to the range observed without CYP 3A4 inducers. However, no clinical data with this dose adjustment in patients receiving strong CYP 3A4 inducers are available. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used before the initiation of the strong CYP 3A4 inducer.

**Drug Interactions.** Everolimus is a substrate of CYP 3A4; it is also a substrate and moderate inhibitor of the multidrug efflux pump Pgp. In *vitro*, everolimus is a competitive inhibitor of CYP 3A4 and a mixed inhibitor of CYP 2D6.

Commentary: Renal cell carcinoma, which develops in the lining of the kidney’s tubules, accounts for approximately 2% of all new cancers. This is the most common type of kidney cancer, and rates are rising steadily around the world partly because of smoking and obesity. Approximately 54,000 new cases of renal cell carcinoma occurred in the U.S. in 2008, and more than 13,000 people died as a result.

Everolimus (5-mg and 10-mg tablets) is the first oral daily therapy for advanced kidney cancer after treatment with sunitinib or sorafenib has failed. Everolimus continuously targets mTOR. This drug is available in different dosage strengths under the trade name Certican (Novartis) for preventing organ rejection in heart and kidney transplant recipients. Certican is approved in Europe, but it is not approved for use in the U.S.

**Sources:** Novartis, www.pharma.us.novartis.com; http://insciences.org

**Ixiaro Vaccine**

**Manufacturer:** Intercell USA, Gaithersburg, Md., and Novartis Pharmaceuticals, East Hanover, N.J.

**Indication:** This intramuscular vaccine is designed to prevent Japanese encephalitis (JE) in persons 17 years of age and older. JE is caused by contact with an infected mosquito. The initial target is adults and military personnel who visit or are deployed to countries, including India, China, and other parts of Asia.

**Drug Class:** Ixiaro vaccine contains a purified, inactivated strain of the JE virus. It is a liquid formulation in a ready-to-use prefilled syringe.

**Uniqueness of Product:** The inactivated vaccine contains the Japanese encephalitis virus (JEV) strain SA14-14-2. It is manufactured with the use of cell culture technology, leading to improved manufacturing efficiency as well as more reliable control of the vaccine-manufacturing process. This technology utilizes an established bank of cells that can be drawn from at any time, thereby helping to ensure consistent quality. It also enhances the ability to rapidly manufacture a vaccine on a large scale, if needed, without compromise to the vaccine’s safety or effectiveness. This attenuated strain has been adapted to grow in Vero cells. The finished product does not contain thimerosal, gelatins, or other stabilizers.

**Warnings and Precautions:**

**Preventing and managing allergic reactions.** Ixiaro vaccine contains protamine sulfate, which can cause hypersensitivity reactions in some individuals. Appropriate medical care should be readily available in case of anaphylactic reaction.

**Limitations of the product’s effectiveness.** Patients who receive only one dose of the vaccine may have a suboptimal response and might therefore incur higher risk if they are exposed to JEV compared with those who receive both doses. Ixiaro vaccine might not result in protection in all cases; for instance, it does not protect against encephalitis caused by viruses or pathogens other than JEV. The full duration of protection following immunization is not known. No data are available about the timing or the efficacy of booster immunization.

**Altered immunocompetence.** No safety or efficacy data are available about the vaccine in immunocompromised individuals, who might have a diminished response to Ixiaro vaccine.

**Adverse Reactions:** Ixiaro vaccine was compared with...
another inactivated JE vaccine (Je-Vax) in a randomized, double-blind clinical trial. No deaths occurred during this trial. One serious adverse event occurred in a subject with a history of myocardial infarction (MI) who experienced an MI three weeks after receiving the second dose of Ixiaro vaccine. Common adverse events were generally mild and included headache, myalgia, influenza-like illness, and fatigue. Local side effects were mild tissue hardening, swelling, and redness at the injection site one week after vaccination. No changes in hematological profiles or clinical chemistry laboratory results were noted.

**Dosage and Administration:** Two doses of the vaccine provided high levels of seroprotection against JEV. Immune responses at 56 days after vaccination, including seroconversion rates and geometric mean titers, were produced. Seroprotection was achieved one week after the second vaccination. One vaccine dose contains 6 mcg of purified, inactivated virus adsorbed to 0.1% aluminum hydroxide. The vaccine, at a dose of 0.5 mL, is injected into the deltoid muscle on days 0 and 28.

**Drug–Drug Interactions:**

**Use with hepatitis A vaccine.** In one trial, Ixiaro vaccine was given with hepatitis A vaccine (Havrix). There was no evidence of interference with the immune response to either vaccine when Havrix was administered concomitantly with the first dose of Ixiaro vaccine. Data are not available on the administration of Ixiaro vaccine with other licensed vaccines made in the U.S. When Ixiaro vaccine is given concomitantly with injectable vaccines, separate syringes should be used at different injection sites. Ixiaro vaccine should not be mixed with any other vaccine in the same syringe or vial.

**Use with immunosuppressive therapies.** There are no data on using Ixiaro vaccine with immunosuppressive therapies, such as irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids.

**Use in Specific Populations:**

**Pregnancy.** The vaccine is classified as a Pregnancy category B product. Studies in rats have revealed no evidence of impaired fertility or harm to the fetus from Ixiaro vaccine; however, no adequate or well-controlled studies have been conducted in pregnant women. This vaccine should be used during pregnancy only if it is clearly needed.

**Nursing mothers.** It is not known whether Ixiaro vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ixiaro vaccine is administered to nursing women.

**Pediatric use.** The safety and effectiveness of Ixiaro vaccine have not been established in patients younger than 17 years of age.

**Geriatric use.** Clinical studies of have not included sufficient numbers of subjects 65 years of age and older to determine whether their responses differ from those of younger subjects.

**Commentary:** As the most important cause of viral encephalitis in Asia, JE is rarely seen in the U.S., and few cases have been reported among civilians and military personnel traveling from the U.S. to Asia. JEV causes at least 50,000 cases of clinical disease every year, mostly in children younger than 10 years of age. The disease is endemic in southeast Asia, a region with more than three billion inhabitants. Within only one month, JE recently killed more than 1,200 children during an epidemic outbreak in India and Nepal.

JE is fatal in approximately 30% of those who show symptoms, and it leaves 50% of survivors with permanent brain damage. Because there is no specific treatment for JE, vaccination is the only effective protection. Prior to its approval, the vaccine was tested in a series of large-scale clinical trials involving almost 5,000 individuals. The total development time of this vaccine from research to approval took more than 10 years.

**Sources:** FDA, March 30, 2009; www.fda.gov; www.medicinenewstoday.com; www.intercell.com

**Recombinant Antithrombin (ATryn) for Injection**

**Manufacturer:** GTC Biotherapeutics, Inc., Framingham, Mass., and Ovation Pharmaceuticals, Deerfield, Ill.

**Indication:** An orphan drug, ATryn is a recombinant antithrombin indicated for the prevention of perioperative and peripartum thromboembolic events in patients with hereditary antithrombin deficiency. It is not indicated for the treatment of thromboembolic events in these patients.

**Drug Class:** ATryn is a 432-amino-acid glycoprotein with a molecular weight of approximately 57,215 daltons. The drug’s amino acid sequence is identical to that of human plasma-derived antithrombin. Both ATryn and plasma-derived antithrombin contain six cysteine residues forming three disulphide bridges and 3-4 N-linked carbohydrate moieties. ATryn’s glycosylation profile differs from that of plasma-derived antithrombin, which results in increased affinity for heparin. When ATryn is assayed in the presence of excess heparin, its potency does not differ from that of the plasma-derived product.

**Uniqueness of Drug:** ATryn is a therapeutic protein derived from the milk of goats that have been genetically engineered by introducing a segment of DNA into their genes with instructions for the goat to produce human antithrombin in its milk. The active moiety in ATryn is a recombinant form of the naturally occurring human antithrombin glycoprotein.

Antithrombin plays a central role in regulating hemostasis. It is the principal inhibitor of thrombin and factor Xa, the serine proteases that play pivotal roles in blood coagulation. It neutralizes the activity of thrombin and factor Xa by forming a complex that is rapidly removed from the circulation. When antithrombin is bound to heparin, the ability of antithrombin to inhibit thrombin and factor Xa can be enhanced by more than 300-fold to 1,000-fold.

**Warnings and Precautions:**

**Hypersensitivity reactions.** Anaphylaxis and severe hypersensitivity reactions are possible with ATryn. If symptoms occur, the product should be discontinued and emergency treatment should be administered.

**Excessive or insufficient anticoagulation.** The anticoagulant effect of drugs that use antithrombin to exert anticoagulation may be altered when ATryn is added or withdrawn. To avoid excessive or insufficient anticoagulation, coagulation tests should be performed that are suitable for the anticoagulant used and at close intervals, especially in the first hours following the start or withdrawal of ATryn. All patients should be monitored for bleeding or thrombosis.

**Dosage and Administration:** ATryn is a sterile lyophilized powder designed for intravenous (IV) use only after reconsti-
tution. Each single-dose vial contains approximately 1,750 IU. The dosage is adjusted for each patient. The goals are to restore and maintain functional antithrombin activity levels between 80% and 120% (0.8–1.2 IU/mL) of normal.

The loading dose is administered as a 15-minute IV infusion, immediately followed by a continuous infusion of the maintenance dose, as shown in Table 1. Monitoring of antithrombin activity is required to ensure proper treatment. Antithrombin activity should be checked once or twice each day, and dose adjustments should be made according to Table 2.

**Adverse Events:** Most common adverse drug events reported included hemorrhage and infusion-site reactions.

**Drug–Drug Interactions:** ATryn enhances the anticoagulant effect of heparin and LMWH. The half-life of ATryn may be altered by concomitant treatment with anticoagulants that use antithrombin to exert their anticoagulant effect.

**Specific Populations:**

- **Pregnant women.** ATryn is a Pregnancy Category C medication. Studies in pregnant women have not shown that ATryn increases the risk of fetal abnormalities if it is given during the third trimester. ATryn is used in the treatment of peripartum women with hereditary antithrombin deficiency.

- **Nursing mothers:** ATryn administered by infusion is present in breast milk at estimated concentrations of 1/50 to 1/100 that of concentration in blood. ATryn should be used only if it is clearly needed.

**Commentary:** ATryn, an anticoagulant, is used to prevent blood clots in patients with hereditary antithrombin deficiency. These patients are at high risk of blood clots during surgery as well as before, during, and after childbirth. ATryn is the first approved biological agent produced by a genetically engineered animal. Hereditary antithrombin deficiency is usually first recognized in teenagers or young adults when clots develop in their blood vessels, particularly during pregnancy, surgery, or prolonged bed rest. Because hereditary antithrombin deficiency occurs in a small population (only 1 in 5,000 people in the U.S.), the FDA granted the product an orphan drug designation. An advisory committee has agreed that ATryn is safe and effective.

**Source:** FDA, www.fda.gov/cber/label/atrynLB.pdf

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**Table 1 ATryn Loading and Maintenance Doses**

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<tr>
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<th>Loading Dose (IU)</th>
<th>Maintenance Dose (IU/Hour)</th>
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<tbody>
<tr>
<td>Surgical patients</td>
<td>(100 – baseline AT activity) × body weight (kg) 2.3</td>
<td>(100 – baseline AT activity) × body weight (kg) 10.2</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>(100 – baseline AT activity) × body weight (kg) 1.3</td>
<td>(100 – baseline AT activity) × body weight (kg) 5.4</td>
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AT = antithrombin; IU = International Units.

**Table 2 Monitoring of ATryn Activity**

<table>
<thead>
<tr>
<th>Initial Monitor Time after Initiating Treatment</th>
<th>Antithrombin Level</th>
<th>Dose Adjustment</th>
<th>Recheck Antithrombin Level</th>
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</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>&lt;80%</td>
<td>Increase 30%</td>
<td>2 hours after each dose adjustment</td>
</tr>
<tr>
<td></td>
<td>80% to 120%</td>
<td>None</td>
<td>6 hours after initiation of treatment or dose adjustment</td>
</tr>
<tr>
<td></td>
<td>&gt;120%</td>
<td>Decrease 30%</td>
<td>2 hours after each dose adjustment</td>
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