Florbetapir F18 (Amyvid)

**Manufacturer:** Avid Radiopharmaceuticals, Philadelphia, Pa./Eli Lilly, Indianapolis, Ind.

**Indication:** Florbetapir F18 is a radioactive diagnostic dye used in positron emission tomography (PET) imaging of the brain to determine the density of beta-amyloid neuritic plaque. The agent is used in adults with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) or other causes of cognitive decline.

**Drug Class:** The chemical formula of florbetapir F18 is (E)-4-(2-(6-(2-(2-(2-[18F] fluoroethoxy) ethoxy) ethoxy)pyridine-3-yl)vinyl)-N-methylbenzamine. The molecular weight is 399.

**Uniqueness of Drug:** This molecular imaging agent binds to beta-amyloid plaque, a sticky, toxic protein. The F18 isotope produces a signal that is detected by a PET scanner during imaging of the brain. In *in vitro* binding studies using postmortem human brain homogenates containing beta-amyloid plaques, the dissociation constant (Kd) for florbetapir was 3.7 ± 0.3 nM. The binding of florbetapir F18 to beta-amyloid aggregates was shown in postmortem human brain sections via autoradiographic methods, thioflavin S, and traditional silver staining correlation studies as well as in monoclonal antibody beta-amyloid correlation studies. Florbetapir F18 binding to tau protein and a battery of neuroreceptors was not detected in *in vitro*.

**Warnings and Precautions:**

**Risk of misinterpretation.** Errors may occur in estimating neuritic plaque density during the interpretation of images. Image interpretation should be performed independently of the patient’s clinical information, which can confound results and lead to errors. Errors in interpretation may also result from extensive brain atrophy, which limits the ability to distinguish gray and white matter on the scan, and from motion artifacts, which distort the image. Florbetapir F18 scan results suggest neuritic amyloid plaque content only during image acquisition. A negative scan, indicating few amyloid clumps, does not preclude the development of brain amyloid in the future.

**Radiation risk.** Like other radiopharmaceuticals, florbetapir F18 contributes to overall cumulative radiation exposure, which may be associated with an increased risk of cancer. Safe handling is required to protect patients and health care workers from unintentional radiation exposure.

**Dosage and Administration:** The recommended dose is 370 megabecquerels (MBq) or 10 millicuries (mCi), not to exceed a 50-mcg dose mass, given as a single intravenous (IV) bolus in a total volume of 10 mL or less. The injection is followed with an IV flush of 0.9% sterile sodium chloride.

The florbetapir F18 dose solution should be inspected before it is administered. The solution should not be used if it contains particulate matter or is discolored. Aseptic technique and radiation shielding are used to withdraw the solution. The dose is assayed in a suitable dose calibrator before administration. Florbetapir F18 is injected through a short IV catheter (1.5 inches or less) to minimize the potential for adsorption of the drug to the catheter. Portions of the dose may adhere to longer catheters. The medication is supplied in 1-mL, 30-mL, or 50-mL multidose vials containing 500 to 1,900 MBq/mL of florbetapir F18.

**Commentary:** The chemical costs $1,600 per dose and is available in limited quantities. Eli Lilly advises that the scan results are not to be used to diagnose AD, because brain plaques can occur naturally in older people with normal mental states; therefore, florbetapir is not indicated in those without memory impairment.

Some experts have questioned the usefulness of the test, because the course of AD is not stopped with currently available drugs. The FDA is also concerned about whether doctors will be able to read the scan results consistently. In March 2011, the agency did not approve the compound, explaining that the company needed to establish a program to train doctors to interpret scan findings accurately.

A negative florbetapir F18 scan indicates few amyloid neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; it also reduces the likelihood that cognitive impairment is caused by AD.

A positive scan indicates moderate-to-widespread plaques but does not establish a diagnosis of AD or other cognitive disorders. In this case, further evaluations are recommended.

Before the development of imaging agents, amyloid plaques could be determined only via an autopsy. In conjunction with other tests, florbetapir F18 has the potential to yield valuable information. The FDA’s approval marks an important advancement in nuclear medicine.


Avanafil (Stendra)

**Manufacturer:** Vivus, Mountain View, Calif.

**Indication:** Avanafil is used for the treatment of erectile dysfunction (ED).

**Drug Class:** This highly selective phosphodiesterase type 5 (PDE5) inhibitor is a synthetic small molecule with one chiral center. The chemical formula is 4-{(3-chloro-4-methoxy-benzyl)amino}-2-{(2-hydroxyethyl)-1-pyrrolidinyl}-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide; (S)-2-(2-hydroxy-methyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-{(2-pyrimidinylmethyl)carbamoy}pyrimidine. The drug’s molecular weight is 483.95.

**Uniqueness of Drug:** Avanafil inhibits a specific PDE5 enzyme, which is present in various body tissues, primarily in the corpus cavernosum penis and in the retina. Avanafil can be synthesized from a benzylamine derivative and a pyrimidine derivative.
PDE₅ inhibitors help to increase blood flow to the penis. Men who were treated with avanafil achieved significant improvement in erectile function compared with those who received placebo. As with other PDE₅ inhibitors, avanafil should not be used by men who also take nitrates for angina, because the combination can cause a sudden drop in blood pressure (BP).

**Warnings and Precautions:**

**Cardiovascular risks.** Therapies for ED, including avanafil, should not be used by men for whom sexual activity is inadvisable because of their underlying cardiovascular status. Patients with left ventricular obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of BP can be particularly sensitive to the action of vasodilators, including avanafil.

The following groups were not included in clinical trials for avanafil: (1) men who had experienced a myocardial infarction (MI), stroke, life-threatening arrhythmia, or coronary revascularization within the previous 6 months; (2) patients with hypertension (below 90/50 mm Hg) or hypertension (above 170/100 mm Hg); (3) patients with unstable angina or angina upon sexual intercourse; and (4) patients with congestive heart failure (New York Heart Association Class 2 or greater).

As with other PDE₅ inhibitors, avanafil has systemic vasodilatory properties and may augment the BP-lowering effect of other antihypertensive medications. An avanafil dose of 200 mg resulted in transient BP of 8.0 mm Hg (systolic) and 3.3 mm Hg (diastolic) in healthy volunteers. The maximum decrease in BP was observed 1 hour after administration. Although this normally would be of little consequence in most patients, before prescribing avanafil, physicians should consider whether patients with underlying cardiovascular disease could be affected adversely by the drug’s vasodilating properties, especially during sexual activity.

**Cytochrome P450 3A4 inhibitors.** Avanafil metabolism is mediated primarily by the CYP isozyme 3A4. Inhibitors of CYP3A4 may reduce avanafil clearance and increase plasma concentrations of avanafil. Patients taking concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, and telithromycin) should not use avanafil.

For patients taking moderate CYP3A4 inhibitors (including erythromycin, amprenavir, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of atazanavir is 50 mg, not to exceed once every 24 hours.

**Prolonged erection.** Erections lasting longer than 4 hours and painful erections lasting longer than 6 hours have been reported with PDE₅ inhibitors. If an erection persists for longer than 4 hours, the patient should seek immediate medical assistance. A delay in treatment may lead to penile tissue damage and permanent loss of potency.

Avanafil should be used with caution in men with anatomical deformation of the penis or in men who have a condition that might predispose them to priapism (e.g., sickle-cell anemia, multiple myeloma, or leukemia).

**Ocular effects.** Patients should be advised to discontinue PDE₅ inhibitors and to seek medical attention if they experience a sudden loss of vision in one or both eyes. A visual event may be a sign of non-arteritis anterior ischemic optic neuropathy (NAION). It is not possible to determine whether this event is directly related to the use of PDE₅ inhibitors or to other factors. Physicians should explain the increased risk of NAION in individuals who have already experienced it in one eye. Patients with a hereditary degenerative retinal disorder were not included in the clinical trials of avanafil; therefore, avanafil is not recommended for these patients.

**Sudden hearing loss.** PDE₅ inhibitors have been associated with a sudden decrease or loss of hearing, which may be accompanied by tinnitus or dizziness. It is not clear whether these events are directly related to the use of this drug class or to other factors. Patients experiencing these symptoms should be advised to stop taking avanafil and should seek prompt medical attention.

**Alpha blockers and other antihypertensive agents.** Physicians should explain the potential for avanafil to augment the BP-lowering effect of alpha blockers and other BP drugs. Caution is advised when PDE₅ inhibitors are administered with alpha blockers. PDE₅ inhibitors, including avanafil, and alpha-adrenergic blocking agents are vasodilators. When vasodilators are used in combination, an additive effect on BP may be anticipated. In some patients, the concomitant use of these two drug classes can lower BP significantly, leading to symptomatic hypotension and fainting.

Before avanafil therapy is initiated, the patient’s BP should be stable with alpha-blocker therapy. Hemodynamic instability with an alpha blocker alone poses an increased risk of symptomatic hypotension with the concomitant use of PDE₅ inhibitors. For patients who are stable with alpha-blocker therapy, avanafil should be initiated at the lowest dose (50 mg).

For patients who are already taking an optimal dose of a PDE₅ inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increases in the alpha-blocker dose may be associated with further lowering of BP during PDE₅ inhibitor therapy. The safety of combining PDE₅ inhibitors and alpha blockers may also be affected by intravascular volume depletion and by other antihypertensive drugs.

**Alcohol.** Patients should be made aware that alcohol and PDE₅ inhibitors act as vasodilators. When vasodilators are taken in combination, the BP-lowering effects of each individual compound may be increased. Therefore, substantial consumption of alcohol (more than 3 units) with avanafil may increase the potential for tachycardia, hypotension, dizziness, and headache.

**Other PDE₅ inhibitors.** The safety and efficacy of combining avanafil with other therapies for ED have not been studied.

**Effect on bleeding.** The safety of avanafil is unknown in patients with bleeding disorders and in patients with peptic ulcers.

**Sexually transmitted diseases.** Avanafil offers no protection against sexually transmitted diseases. Clinicians should consider counseling patients about protective measures necessary to guard against sexually transmitted diseases, including HIV infection.

**Dosage and Administration:** The recommended starting dose of oral avanafil is 100 mg. The drug is taken, as needed, approximately 30 minutes before sexual activity. Depending on individual efficacy and tolerability, the dose can be varied to a maximum of a 200-mg tablet or decreased to a 50-mg tablet. The lowest dose that provides efficacy should be used. The rec-
ommended maximum dosing frequency is once per day.

Commentary: ED can affect men more as they grow older. Up to 40% of men may experience ED at age 40, and 65% of men experience it after age 65. ED affects 1 in 10 men worldwide and 15 to 30 million men in the U.S.

Similar drugs indicated for ED include sildenafil (Viagra, Pfizer), tadalafl (Cialis, Eli Lilly), and vardenafin (Levitra, Bayer/GlaxoSmithKline). An advantage of avanafil is the relatively short time it takes to start working (30 minutes or less). It usually takes between 30 minutes and 12 hours before tadalafl becomes effective and more than 30 minutes for full plasma concentrations to be reached. Sildenafil and vardenafin are taken about 1 hour before sexual activity. Avanafil’s short time to effectiveness may be its key benefit in a market that already has a supply of ED medications. Finally, avanafil stays in the blood for a shorter time, which has the potential to lead to fewer adverse effects compared with other treatments.

Source: www.stendra.com

**Peginesatide Injection (Omontys)**

**Manufacturer:** Affymax, Palo Alto, Calif./Takeda, Osaka, Japan

**Indication:** Peginesatide is indicated for the treatment of anemia caused by chronic kidney disease (CKD) in adults receiving dialysis.

**Drug Class:** Peginesatide, a synthetic, pegylated, dimeric erythropoiesis-stimulating agent (ESA), is the only ESA that is peptide-based. Its amino acids are arranged in an order that differs from that of erythropoietin; it has no sequence homology to endogenous erythropoietin. Made from an acetate salt, peginesatide comprises two identical, 21-amino-acid chains covalently bonded to a molecular chain derived from iminodiacetic acid and beta-alanine. The dimeric peptide (molecular weight, 900 daltons) is covalently linked to a single lysine-diacetic acid and beta-alanine. The dimeric peptide (molecular weight, about 40,000 daltons). The empirical formula is C₂₀₃¹H₃₉₅₀N₆₂O₉₅₈S₆ (free base).

**Uniqueness of Drug:** Peginesatide aids in the formation of red blood cells (RBCs) by stimulating bone marrow, thus helping to reduce the need for transfusions in patients with CKD.

**Boxed Warning:** ESAs may increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.

**Chronic kidney disease.** In controlled trials, patients experienced a higher risk of death, serious adverse cardiovascular reactions, and stroke when they received ESAs to a target hemoglobin level above 11 g/dL. No trials have identified a hemoglobin target level, an ESA dose, or a dosing strategy that does not increase these risks. The lowest dose sufficient to reduce the need for RBC transfusions should be used.

**Warnings and Precautions:**

- **Risk of death, MI, stroke, and thromboembolism.** Using ESAs to target a hemoglobin level exceeding 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Caution should be used in patients with coexistent cardiovascular disease and stroke. Patients with CKD who have had an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and death than other patients. A hemoglobin elevation of more than 1 g/dL over a period of 2 weeks may contribute to these risks.

- In clinical trials of ESAs in patients with cancer, an increased risk of death and serious adverse cardiovascular reactions (MI, stroke) was observed.

- In clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery and raised the risk of deep venous thrombosis in patients undergoing orthopedic procedures. In two trials of peginesatide, patients with CKD who were not receiving dialysis experienced an increased rate of cardiovascular events.

**Risks of death, tumor progression, or tumor recurrence in cancer patients.** The safety and efficacy of peginesatide have not been established for use in patients with anemia caused by cancer chemotherapy. Peginesatide is not indicated in patients receiving chemotherapy.

**Hypertension.** Peginesatide is contraindicated in patients with uncontrolled hypertension. BP should be controlled before and during therapy, and the medication should be withheld if BP becomes difficult to control. Patients should be advised of the importance of complying with antihypertensive therapy and dietary restrictions.

**Lack or loss of response to peginesatide.** If a hemoglobin response to peginesatide is lost or absent, the cause should be sought. If the usual causes are excluded, the patient should be evaluated for the presence of antibodies to peginesatide.

**Dialysis management.** Patients receiving peginesatide may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

**Laboratory monitoring.** Transferrin saturation and serum ferritin levels should be evaluated before and during peginesatide treatment. Supplemental iron may be needed if the serum ferritin exceeds 100 mcg/L or if serum transferrin saturation is higher than 20%.

**Dosage and Administration:** Peginesatide is administered either intravenously or subcutaneously as a single monthly injection. As an initial treatment, peginesatide should be given once monthly as 0.04 mg/kg of body weight.

**Contraindications:** Peginesatide should not be given to patients with uncontrolled hypertension.

**Commentary:** Anemia is a common complication in CKD patients receiving dialysis because their kidneys do not produce enough erythropoietin, which stimulates RBC production. As of 2012, almost 400,000 people in the U.S. are on dialysis, reports the U.S. Renal Data System. According to the Centers for Medicaid & Medicare Services, nearly 95% of dialysis patients in the U.S. are being treated for anemia with ESAs.

Peginesatide is the only once-monthly ESA for anemia available to dialysis patients in the U.S. It is not indicated for patients with CKD who are not on dialysis, patients receiving chemotherapy, patients whose anemia is not caused by CKD, or patients who require immediate correction of anemia. Peginesatide is not a substitute for RBC transfusions, and it has not been shown to improve symptoms, physical functioning, or health-related quality of life. Adverse effects may include diarrhea, nausea, vomiting, back pain, cough, and muscle spasms.

Sources: FDA, March 27, 2012; www.fda.gov; www.omontys.com