**Pharmaceutical Approval Update**

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**Aliskiren/Amlodipine Tablets (Tekamlo)**

**Manufacturer:** Novartis, Florham Park, N.J.

**Indication:** The combination of aliskiren and amlodipine is intended for the treatment of hypertension (1) as initial therapy in patients likely to need multiple drugs to achieve normal blood pressure (BP) goals, (2) in patients whose BP is not adequately controlled with monotherapy, and (3) as a substitute for its titrated components.

**Drug Class:** Aliskiren hemifumarate (Tekturna, Novartis) is an orally active, nonpeptide, potent direct renin inhibitor. It is chemically described as (2S, 4S,5S,7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-di-isopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate. Its molecular weight is 609.8 (free base, 551.8).

Amlodipine besylate (Norvasc, Pfizer) is a dihydropyridine calcium-channel blocker. Its chemical name is 3-ethyl 5-methyl (±)-2-(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate. Its molecular weight is 567.1.

Aliskiren/amlodipine tablets are available in strengths of 150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg, and 300 mg/10 mg.

**Uniqueness of Product:**

**Aliskiren.** Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways.

Ang II is a powerful vasoconstrictor that leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase BP. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin–angiotensin–aldosterone system (RAAS). Aliskiren decreases plasma renin activity and inhibits the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components (e.g., ACE or non-ACE pathways) is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentrations. When this elevation occurs during treatment with ACE inhibitors and angiotensin-receptor blockers (ARBs), plasma renin activity is increased. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that plasma renin activity, Ang I, and Ang II are all reduced with aliskiren alone or with other antihypertensive agents.

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**Amlodipine.** Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that it binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle depend on the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine selectively blocks calcium ion influx across cell membranes and has a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro, but such effects have not been seen in intact animals at therapeutic doses. Amlodipine does not affect serum calcium levels. As a peripheral arterial vasodilator, it acts directly on vascular smooth muscle to reduce peripheral vascular resistance and BP.

**Tekamlo.** The effects of combining aliskiren and amlodipine arise from the actions of these two agents on different but complementary mechanisms that regulate BP, calcium-channel–mediated vasoconstriction, and RAAS-mediated effects on vascular tone and sodium excretion.

**Boxed Warning:** Tekamlo should be avoided in pregnancy. If pregnancy is detected, the drug should be discontinued as soon as possible. Drugs that act directly on the RAAS can cause injury and even death to the developing fetus.

**Warnings and Precautions:**

**Fetal and neonatal morbidity and mortality.** Drugs that act directly on the RAAS during pregnancy can cause fetal and neonatal morbidity and death. No animal studies were conducted with Tekamlo; however, decreased fetal birth weight was observed in animal studies of aliskiren, and intraperitoneal deaths were observed in animal trials of amlodipine. Tekamlo can cause fetal harm and should be discontinued as soon as possible if pregnancy is confirmed. If Tekamlo is used during pregnancy or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

**Head and neck angioedema.** Patients receiving aliskiren have experienced angioedema of the face, extremities, lips, tongue, glottis, or larynx and have required hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with or without a history of angioedema who received ACE inhibitors or ARBs. If angioedema involves the throat, tongue, glottis, or larynx or if the patient has had surgery of the upper respiratory tract, airway obstruction may occur and may be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation, because antihistamines and corticosteroids might not be sufficient to prevent respiratory problems. Prompt administration of subcutaneous (SQ) epinephrine solution 1:1000 (0.3 to 0.5 mL) and measures to ensure a patent airway may be necessary. If angioedema occurs, Tekamlo should be stopped immediately and should not be given again.

**Hypotension.** In controlled trials, hypotension was rarely seen (0.2%) in patients with uncomplicated hypertension when
they used Tekamlo. In patients with an activated RAAS (e.g., with volume or salt depletion) who received high doses of diuretics, symptomatic hypotension occurred with RAAS blockers. These conditions should be corrected before Tekamlo is given, or therapy should be given under medical supervision. If hypertension occurs with Tekamlo, the patient should be placed in the supine position and, if necessary, should receive an intravenous (IV) infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty after BP has stabilized.

**Myocardial infarction or increased angina.** Rarely has initiating or changing the dose of a calcium-channel blocker resulted in an increased frequency, duration, or severity of angina or acute myocardial infarction (MI), particularly in patients with severe obstructive coronary artery disease.

**Impaired renal function.** Clinical trials of Tekamlo have excluded patients with severe renal impairment. Trials of aliskiren in hypertension have excluded patients with severe renal dysfunction (i.e., creatinine, 1.7 mg/dL for women and 2 mg/dL for men, or an estimated glomerular filtration rate of less than 30 mL/minute). Patients have also been excluded if they have had dialysis, nephrotic syndrome, or renovascular hypertension. Serum electrolytes should be measured periodically to detect any electrolyte imbalances.

**Hepatic impairment.** Amlodipine is metabolized extensively by the liver. The plasma elimination half-life is 56 hours in patients with impaired hepatic function; therefore, caution is required when heptatically impaired patients use Tekamlo.

**Congestive heart failure.** Amlodipine 5 to 10 mg/day was studied in a placebo-controlled trial of 1,153 patients with New York Heart Association (NYHA) Class III or IV heart failure. Patients received stable doses of an ACE inhibitor, digoxin, and a diuretic. The follow-up period was at least six months (mean, 14 months). There was no overall adverse effect on survival or cardiac morbidity (i.e., a life-threatening arrhythmia, acute MI, or hospitalization for worsened heart failure). When amlodipine was compared with placebo in four 8- to 12-week studies of 687 patients with NYHA Class II/III heart failure, there was no evidence of worsening heart failure based on exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction.

**Renal artery stenosis.** No data are available on Tekamlo or aliskiren in patients with unilateral or bilateral renal artery stenosis or arterial stenosis of a solitary kidney. However, in studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, elevated serum creatinine or blood urea nitrogen levels have been reported.

**Cyclosporine.** When aliskiren was given with cyclosporine, serum levels of aliskiren were significantly increased. The concomitant use of Tekamlo with cyclosporine is not recommended.

**Dosage and Administration:** BP-lowering effects are usually attained within one to two weeks.

**Initial therapy and dose titration.** The usual recommended starting dose of Tekamlo is 150 mg/5 mg once daily, as needed, to control BP. If BP remains uncontrolled after two to four weeks of therapy, the dose is titrated to a maximum of 300 mg/10 mg once daily. Tekamlo is not recommended as initial therapy in patients with intravascular volume depletion.

**Add-on therapy.** Tekamlo is used when BP is inadequately controlled with aliskiren alone or with amlodipine alone. Patients experiencing dose-limiting adverse reactions with either aliskiren or amlodipine alone can be switched to a Tekamlo formulation that contains a lower dose of both ingredients to achieve similar BP reductions.

**Replacement therapy.** Patients receiving aliskiren and amlodipine from individual tablets can be switched to a single tablet of Tekamlo containing the same component doses. When substituting for the individual agents, the clinician can increase the dose of one or both of the ingredients if BP control has not been satisfactory.

**Other antihypertensive drugs.** Tekamlo may be used with other antihypertensive agents. It is not known whether aliskiren (Tektarna) decreases BP further when it is added to maximum dosages of ACE inhibitors and beta blockers.

**Commentary:** Tekamlo combines a direct renin inhibitor (aliskiren) with a calcium-channel blocker (amlodipine) in a single tablet and significantly reduces BP compared with either agent alone. Up to 85% of patients may need multiple medications to help control BP, underscoring the need for effective combination treatments. Tekamlo is approved as initial therapy for patients who are likely to need multiple drugs to achieve BP goals and as replacement therapy when BP is not adequately controlled with either drug alone. The effects of combined treatment arise from the actions of the two agents on different but complementary mechanisms.

**Source:** www.pharma.us.novartis

**Bimatoprost Ophthalmic Solution 0.01% (Lumigan)**

**Manufacturer:** Allergan, Inc., Irvine, Calif.

**Indication:** Bimatoprost, an optimized reformulation of the previously approved 0.03% solution, is a first-line therapy indicated for lowering intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

**Drug Class:** This solution is a synthetic structural analogue of prostaglandin with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]-5-(N-ethylheptanenamide, and its molecular weight is 415.58. The molecular formula is C_{36}H_{57}NO_{14}.

**Uniqueness of Product:** Bimatoprost selectively mimics the effects of naturally occurring substances (prostagrandins). It appears to reduce IOP in humans by increasing the outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the IOP, the greater the likelihood of optic nerve damage and visual field loss.

**Warnings and Precautions:**

**Pigmentation.** Bimatoprost can cause changes in the pigmented tissues (e.g., the iris, eyelids, and eyelashes). Pigmentation is expected to increase as long as bimatoprost is given. After patients stop using the solution, pigmentation of the iris is likely to be permanent, but pigmentation of the peribulbar tissue and eyelash changes may be reversible. Patients should be informed of the possibility of increased pigmentation. Color changes in the iris might not be noticeable for several months to years. Typically, the brown pigmentation...
around the pupil spreads concentrically toward the periphery of the iris, and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by therapy. The solution can be continued if noticeably increased iris pigmentation occurs. If pigmentation does increase, patients should be examined regularly.

**Eyelash changes.** Both formulations (0.01% and 0.03%) may gradually affect eyelashes and vellus hair in the treated eye. Changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

**Intraocular inflammation.** Bimatoprost 0.01% and 0.03% should be used with caution in patients with uveitis because the inflammation may be exacerbated.

**Macular edema.** Macular edema and cystoid macular edema have been reported during treatment. Bimatoprost 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with risk factors for macular edema.

**Glaucoma.** Neither the 0.01% and nor the 0.03% solution has been evaluated for the treatment of angle-closure, inflammatory, or neovascular glaucoma.

**Bacterial keratitis.** Bacterial keratitis has been associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who usually had a concurrent corneal disease or a disruption of the ocular epithelial surface.

**Use with contact lenses.** Contact lenses should be removed before bimatoprost is instilled. The lenses may be reinserted 15 minutes after the solution is administered.

**Dosage and Administration:** The recommended dosage is one drop in the affected eye once daily in the evening. Bimatoprost 0.01% and 0.03% should not be administered more than once daily; more frequent administration of prostaglandin analogues may decrease the IOP-lowering effect. IOP starts to decrease approximately four hours after the first administration, and the maximum effect is reached within eight to 12 hours. Bimatoprost may be used concomitantly with other topical ophthalmic products to lower IOP. If more than one topical ophthalmic agent is being used, each drug should be administered at least five minutes apart.

**Commentary:** The new strength of Lumigan 0.1 mg/mL (0.01%) solution was developed as an alternative to the previously approved Lumigan 0.3 mg/mL (0.03%) eyedrops. Lumigan 0.03% contains 0.3 mg/mL of bimatoprost and 50 parts per million (ppm) of benzalkonium chloride. The new strength contains one-third the concentration of bimatoprost (0.1 mg/mL) and 200 ppm of benzalkonium chloride. The higher concentration of benzalkonium chloride increases the ocular absorption of bimatoprost, thus allowing for a lower concentration of bimatoprost to be used (0.1 mg/ml). This new formulation, with a reduced concentration of bimatoprost, achieves similar IOP-lowering efficacy and an improved overall safety profile.

Bimatoprost is a prostamide, a synthetic analogue of fatty acid amides rather than a true prostaglandin. It is unknown whether this slight structural difference is clinically apparent.

The most commonly reported adverse effect of bimatoprost is conjunctival hyperemia. The release of nitric oxide by the prostaglandin analogue may cause this hyperemia, although this effect is neither well understood nor proven. Ocular adverse events with bimatoprost 0.01% include conjunctival hyperemia, erythema of eyelid, eye irritation, growth of eyelashes, eye pruritus, eye pain, and abnormal sensation in the eye. Most ocular adverse events have been of mild severity.

Bimatoprost does not appear to have a phototoxic potential. It penetrates the human cornea and sclera in vitro. After ocular administration, the systemic exposure of bimatoprost is very low, with no accumulation over time.

The proposed mechanisms for the side effects of bimatoprost and other prostaglandin analogues do not appear to be a factor in causing deepening of the lid sulcus. It is possible that Mueller’s muscle is affected by the prostamide, yet palpebral fissure measurements do not appear to change with the induction or removal of the drug.

In 2008, the FDA also approved bimatoprost as a cosmetic agent (Latisse) for lengthening the eyelashes.


**Hexaminolevulinate HCl for Intravesical Solution (Cysview)**

**Manufacturer:** GE Healthcare, Princeton, N.J.

**Indication:** Cysview is used in cystoscopy to detect non-muscle, invasive papillary cancer of the bladder among patients thought to have lesions on the basis of a prior cystoscopy. This agent is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the “blue light” setting (Mode 2) as an adjunct to the “white light” setting (Mode 1). Cysview is not a replacement for random bladder biopsies or other procedures used for detecting papillary bladder cancer, and it is not indicated for repetitive use.

**Drug Class:** As an optical imaging drug in solution form, Cysview is instilled intravesically. The molecular formula is C_{11}H_{21}NO_{3} · HCl, and its molecular weight is 251.76.

**Uniqueness of Product:** Cysview is an ester of the heme precursor, aminolevulinic acid. After bladder instillation, the product enters the bladder mucosa and is thought to enter the intracellular space of mucosal cells, where it is used as a precursor in the formation of the photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs). PpIX and PAPs accumulate in neoplastic cells, more than in normal urothelium, partly a result of altered enzymatic activity in the neoplastic cells. After excitation with light at wavelengths between 360 and 450 nanometers (nm), PpIX and other PAPs return to a lower energy level by fluorescing, which can be detected and used in cystoscopic detection of lesions. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Similar processes may occur in inflamed cells. In vitro studies have shown increased porphyrin fluorescence in normal urothelium after exposure to Cysview. In the human bladder, porphyrins tend to amass in neoplastic or inflamed cells.

**Warnings and Precautions: Anaphylaxis.** Anaphylactoid shock has been reported with Cysview. Before and during use, trained personnel should be available in case of an anaphylactic reaction. The safety of continued on page 582
repeated exposures with Cysview has not been evaluated.

**Failed detection.** Clinicians using Cysview might miss some bladder tumors, including malignant lesions. Cysview does not replace biopsies or other procedures used to evaluate the presence of cancer. In a controlled clinical trial, 10% of lesions confirmed as malignant within the study drug group were missed with Cysview. Cystoscopy should not be used with blue light alone, because malignant lesions can be overlooked unless the bladder is initially examined under white light.

**False fluorescence.** Fluorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. In the controlled clinical study, biopsies from one of every four fluorescent areas showed neither dysplasia nor carcinoma if the areas were not also identified during white light cystoscopy. In addition to these false detections, fluorescent areas within the bladder mucosa may result from inflammation, cystoscopic trauma, scar tissue, or bladder mucosal biopsy from a previous cystoscopic examination.

The presence of urine or blood within the bladder may interfere with the detection of tissue fluorescence. To enhance the diagnostic utility of Cysview with the Karl Storz system, the bladder should be emptied of urine before fluids are instilled during cystoscopy. Biopsy or bladder resection of mucosal lesions should be performed only after both white light and blue light cystoscopy.

**Dosage and Administration.** The recommended dose of Cysview for adults is 50 mL of reconstituted solution, instilled into the bladder via a urinary catheter.

**Reconstitution.** Cysview is supplied as a kit containing two vials. A clear glass vial, labeled as Cysview for Intravesical Solution, holds 100 mg of hexaminolevulinate HCl as a powder. A propylene vial contains 50 mL of the diluent.

**Instillation.** Straight or intermittent urethral catheters with a proximal funnel opening are used to accommodate the Luer Lock adapter. Only catheters made of vinyl (uncoated or coated with hydrogel), latex (amber or red), and silicone are used to instill the reconstituted solution. Catheters coated or embedded with silver or antibiotics should not be used. Indwelling bladder (Foley) catheters may be used if they are inserted shortly before Cysview is administered, and they are removed following drug instillation.

**Storz system.** Imaging with Cysview requires the use of the Storz diagnostic system, which consists of a light source, a camera, and a telescope. The light source enables both white light cystoscopy and blue light (wavelength 360–450 nm) fluorescence cystoscopy. Clinicians must be familiar with this system before instilling Cysview into the bladder. Proficiency in cystoscopic procedures is essential prior to using Cysview.

**Commentary:** Cysview is an optical imaging agent indicated for use with cystoscopy to detect non-muscle, invasive papillary cancer of the bladder. The device is used with the Storz system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1). The use of Cysview and blue light cystoscopy enables more accurate detection of tumors than with standard white light technology.