Oxybutynin Transdermal System (Oxytrol for Women)

Manufacturer: Watson/Merck, Parsippany, N.J.

Indication: The oxybutynin patch is indicated for the treatment of overactive bladder in women with symptoms of urge urinary incontinence, urgency, and frequency. Women may buy the product over the counter, but men still need a prescription for oxybutynin tablets.

Drug Class: As a muscarinic antagonist and an antispasmodic anticholinergic agent, oxybutynin is administered as a racemate of R- and S-isomers. Chemically, oxybutynin is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate. The empirical formula is C₂₂H₃₁NO.

Uniqueness of Drug: The oxybutynin transdermal system is designed to deliver medication over a 3- to 4-day interval after it is applied to intact skin. The matrix-type system is composed of three layers. Layer 1 (the backing film) is made of thin, flexible polyester/ethylene-vinyl acetate and provides occlusivity and physical integrity to protect the adhesive (drug) layer (layer 2). The drug layer is a cast film of acrylic adhesive containing oxybutynin and triacetin USP. Layer 3 (the release liner) is composed of two overlapped siliconized polyester strips that the patient peels off and discards before she applies the matrix system.

Warnings and Precautions:

Urinary retention. Oxytrol should be administered with caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Gastrointestinal disorders. Patients with gastrointestinal (GI) obstructive disorders (such as ulcerative colitis or intestinal atony) should use caution when using oxybutynin because of the risk of gastric retention. Like other anticholinergic drugs, oxybutynin may decrease GI motility. It should be used with caution in patients with gastroesophageal reflux disease (GERD) and in those who are concurrently taking other drugs that can cause or exacerbate esophagitis, such as bisphosphonates.

Central nervous system effects. Products containing oxybutynin are associated with anticholinergic effects on the central nervous system (CNS). Patients should be monitored for signs of headache, dizziness, and somnolence, especially after they begin treatment. If a patient experiences anticholinergic CNS effects, the clinician should consider recommending that the drug be discontinued. Clinicians should advise patients not to drive or operate heavy machinery until they know how the patch affects them.

Angioedema. Angioedema requiring hospitalization and emergency medical treatment have occurred with the first or subsequent doses of oral oxybutynin. If angioedema occurs, the patch should be discontinued and appropriate therapy should be promptly provided.

Skin hypersensitivity. If skin hypersensitivity develops, oxybutynin treatment should be discontinued.

Exacerbation of myasthenia gravis. Oxybutynin should be administered with caution to patients with myasthenia gravis, which is characterized by decreased cholinergic activity at the neuromuscular junction.

Dosage and Administration: Oxytrol for Women is available as a 39-cm² transdermal system containing 36 mg of oxybutynin. The nominal in vivo delivery rate is 3.9 mg/day. The patch should be applied to dry, intact skin on the abdomen, hip, or buttock twice weekly (every 3 or 4 days). A new application site should be selected with each new patch to avoid reapplication to the same site within 7 days.

Commentary: More than 33 million Americans, 20 million of whom are women, have overactive bladder. Oxytrol for Women is the first transdermal system approved for this indication. Oxybutynin has been prescribed in oral formulations for almost 30 years. The patch enables the drug to be delivered into the patient’s bloodstream, bypassing the initial metabolic process in the liver and the stomach. The patch has the potential to offer continuous urinary bladder control with a low incidence of adverse effects, such as dry mouth and constipation. The criteria for diagnosing OAB are not standardized, and the severity of symptoms varies widely.

Sources: www.mercknewsroom.com; http://pi.actavis.com

Alogliptin Tablets (Nesina, Kazano, and Oseni)

Manufacturer: Takeda, Deerfield, Ill./Furiex Pharmaceuticals, Morrisville, N.C.

Indication: Three formulations of alogliptin are approved to improve blood glucose control, along with diet and exercise, in adults with type-2 diabetes: alogliptin (Nesina), alogliptin/metformin HCl (Kazano), and alogliptin/pioglitazone (Oseni). Alogliptin is not intended for patients with type-1 diabetes or diabetic ketoacidosis.

Drug Class: This is the fourth FDA-approved selective dipeptidyl peptidase IV (DPP-4) inhibitor, joining sitagliptin (Januvia, Merck), saxagliptin (Onglyza, Bristol-Myers Squibb/AstraZeneca), and linagliptin (Tradjenta, Boehringer Ingelheim) for patients with type-2 diabetes. Alogliptin is prepared as a benzoate salt, 2-[6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl]methyl benzonitrile monobenzoate. The molecular weight is 461.51 daltons.

Uniqueness of Drug: Alogliptin slows the inactivation of the incretin hormones, thereby increasing serum levels and reducing fasting and postprandial glucose levels in a glucose-dependent manner. Nesina (alogliptin) selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures. Kazano combines alogliptin and metformin, a biguanide. Oseni (alogliptin/pioglitazone) is the first medication that includes a DPP-4 inhibitor and a thiazolidinedione (TZD) in a single tablet.
Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause the release of insulin from the pancreatic beta cells in a glucose-dependent manner, but they are inactivated by the DPP-4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type-2 diabetes, GLP-1 levels are reduced but the insulin response to GLP-1 is preserved.

**Nesina (Alogliptin)**

**Boxed Warning:** Alogliptin (Nesina) is contraindicated in patients with a history of serious hypersensitivity reactions (anaphylaxis, angioedema, or severe cutaneous adverse reactions) to any of the drug’s components.

**Warnings and Precautions:**

**Acute pancreatitis.** There have been postmarketing reports of acute pancreatitis with alogliptin. If pancreatitis is suspected, treatment should be discontinued promptly.

**Hypersensitivity.** Postmarketing reports have mentioned serious hypersensitivity reactions in patients treated with alogliptin such as anaphylaxis, angioedema, and severe cutaneous adverse reactions. If these events occur, therapy should be stopped immediately. The patient should be evaluated for any other possible causes. Appropriate monitoring and treatment should be conducted, and an alternative treatment for diabetes should be initiated. Caution is advised for patients with a history of angioedema resulting from another DPP-4 inhibitor, because it is not known whether these patients will be predisposed to angioedema while taking alogliptin.

**Hepatic effects.** There have been postmarketing reports of hepatic failure, sometimes fatal, with alogliptin. A baseline liver test panel is recommended. If liver injury is detected, treatment with Nesina should be interrupted and the patients should be evaluated for a probable cause. If possible, the cause of the liver injury should be treated until the problem is resolved or the patient is stabilized. Therapy should not be resumed if liver injury is confirmed and if no other cause is found. Alogliptin should be prescribed with caution in patients with liver disease.

**Hypoglycemia.** Insulin and insulin secretagogues can cause hypoglycemia. A lower dose of the insulin or the insulin secretagogue may be required to minimize the risk when used in combination with Nesina.

**Macrovascular risk.** No clinical studies have shown conclusive evidence of macrovascular risk reduction with alogliptin or any other antidiabetic drug.

**Dosage and Administration:** The recommended dose of alogliptin (Nesina) is 25 mg once daily with or without food. Nesina 25-mg tablets are light red, oval, biconvex, and film-coated. The 12.5-mg tablets are yellow, and the 6.25-mg tablets are light pink.

For patients with mild renal impairment, defined as a creatinine clearance (CrCl) of 60 mL or more per minute, no dose adjustments are necessary.

For patients with moderate renal impairment, defined as a CrCl between 30 and 60 mL/minute, the dose is 12.5 mg once daily.

For patients with severe renal impairment, defined as a CrCl between 15 and 30 mL/minute, for those with end-stage renal disease (a CrCl of less than 15 mL/minute), or for those requiring hemodialysis, the dose is 6.25 mg once daily.

Nesina may be administered without regard to the timing of dialysis. This drug has not been studied in patients undergoing peritoneal dialysis. Assessment of renal status is recommended before therapy begins and periodically thereafter because dosage adjustments may be necessary, depending on kidney function.

**Kazano (Alogliptin/Metformin)**

**Boxed Warning:** Lactic acidosis is a rare but serious complication that can result from the accumulation of metformin (Glucophage, Bristol-Myers Squibb). The risk increases with sepsis, dehydration, excessive alcohol intake, hepatic and renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and abdominal distress. Laboratory abnormalities include low pH, an increased anion gap, and elevated serum lactate levels. If acidosis is suspected, alogliptin/metformin should be discontinued and the patient should be hospitalized immediately.

**Warnings and Precautions:**

**Lactic acidosis.** Patients should be warned to avoid excessive alcohol intake during treatment. Kazano is not recommended in patients with hepatic or renal impairment. Renal function should be normal before treatment begins and should be confirmed to be normal at least annually thereafter. Treatment should be temporarily discontinued in patients undergoing radiological studies with intravascular iodinated contrast materials or in those having surgery calling for a restricted intake of food and fluids.

Lactic acidosis resulting from metformin accumulation during therapy is fatal in approximately 50% of cases. The risk increases in patients with renal impairment, congestive heart failure requiring drug treatment, and increasing age.

**Vitamin B12 deficiency.** Metformin may lower vitamin B12 levels. Hematological parameters should be monitored annually.

**Acute pancreatitis:** There have been postmarketing reports of acute pancreatitis with Kazano. If pancreatitis is suspected, treatment should be discontinued promptly.

**Hypersensitivity.** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Kazano, such as anaphylaxis, angioedema, and severe cutaneous adverse reactions. In such cases, the combination should be discontinued and the patient should be evaluated for other possible causes of hypersensitivity. Appropriate monitoring and treatment should be instituted, and an alternative diabetes treatment should be selected. Caution is advised for patients with a history of angioedema resulting from the use of another DPP-4 inhibitor, because it is not known whether such patients will be predisposed to angioedema.

**Hepatic effects.** Hepatic failure, sometimes resulting from the accumulation of metformin (Glucophage, Bristol-Myers Squibb). The risk increases with sepsis, dehydration, excessive alcohol intake, hepatic and renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and abdominal distress. Laboratory abnormalities include low pH, an increased anion gap, and elevated serum lactate levels. If acidosis is suspected, alogliptin/metformin should be discontinued and the patient should be hospitalized immediately.
possible, to resolution or stabilization. Treatment should not be restarted if liver injury is confirmed and if no other cause is found. Alogliptin/metformin should be prescribed with caution in patients with liver disease.

**Hypoglycemia.** Insulin and insulin secretagogues can cause hypoglycemia. A lower dose of the insulin or insulin secretagogue may be required to minimize the risk when used in combination with alogliptin/metformin.

**Macrovascular risk.** No clinical studies have established conclusive evidence of macrovascular risk reduction with alogliptin/metformin or any other antidiabetic drug.

**Dosage and Administration:** Clinicians should tailor the starting dose of alogliptin/metformin (Kazano) according to the patient’s current regimen. Tablets should be taken twice daily with food, and the dose should be gradually escalated to reduce any gastrointestinal (GI) adverse effects resulting from metformin.

The tablets should not be split before swallowing. The dosage may be adjusted according to effectiveness and tolerability as long as it does not exceed the maximum recommended daily dose of 25 mg of alogliptin and 2,000 mg of metformin.

Kazano is available as pale yellow, oblong, film-coated tablets in two strengths: alogliptin 12.5 mg/metformin 500 mg and alogliptin 12.5 mg/metformin 1,000 mg.

**OSENi (ALGOLIPTIN/PioglITAZONE)**

**Boxed Warning:**

*Congestive heart failure.* Thiazolidinediones, including pioglitazone (Actos, Takeda/Eli Lilly), can cause or exacerbate congestive heart failure (CHF) in some patients. After alogliptin/pioglitazone therapy is initiated and after dose increases, patients should be carefully monitored for signs and symptoms of CHF (e.g., excessive or rapid weight gain, dyspnea, or edema). If CHF develops, it should be managed according to current standards of care; the dose of pioglitazone in Oseni should be reduced or stopping pioglitazone should be considered.

Oseni is not recommended in patients with symptomatic heart failure, and it is contraindicated in patients with established New York Heart Association (NYHA) Class III or IV CHF.

**Pancreatitis.** Alogliptin may cause pancreatitis. Patients should inform their physician about whether they have ever had pancreatitis; gallstones; or a history of alcoholism, kidney problems, or liver problems. If persistent stomach pain occurs with treatment, patients should inform their physician immediately; this pain can be a symptom of pancreatitis.

**Warnings and Precautions:**

*Congestive heart failure.* Fluid retention may occur with treatment and can worsen or lead to CHF. The use of insulin with the combination in patients with NYHA Class I and II CHF may increase the risk. Patients should be monitored for excessive or rapid weight gain, dyspnea, or edema.

**Edema.** Dose-related edema may occur with Oseni. This medication should be prescribed with caution in patients with edema.

**Fractures.** An increased incidence of fractures has been observed in women receiving Oseni. Clinicians should apply current standards for assessing and maintaining bone health.

**Bladder cancer.** Data suggest an increased risk of bladder cancer in patients who use pioglitazone, with the risk increasing with duration of use. Oseni should not be prescribed for patients with present or past bladder cancer.

Patients should be counseled to report hematuria, dysuria, or urinary urgency immediately, because these may be a result of bladder cancer.

**Macular edema.** Macular edema has been reported in some patients taking pioglitazone. Regular eye examinations are recommended, and patients should be advised to report any visual changes promptly.

**Ovulation.** Pioglitazone may result in ovulation in some premenopausal anovulatory women.

**Acute pancreatitis.** There have been postmarketing reports of acute pancreatitis with pioglitazone. If pancreatitis is suspected, Oseni should be promptly discontinued.

**Hypersensitivity.** Postmarketing reports have mentioned serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, or severe cutaneous adverse reactions) with alogliptin. In such cases, Oseni should be discontinued and the patient should be evaluated for other possible causes.

Appropriate monitoring and treatment should be instituted, and an alternative therapy for diabetes should be provided. Caution should be used in patients with a history of angioedema after using another DPP-4 inhibitor; it is unknown whether such patients will be predisposed to angioedema.

**Hepatic effects.** There have been postmarketing reports of hepatic failure with Oseni, sometimes fatal. A baseline liver test panel is recommended. If liver injury is detected, Oseni therapy should be interrupted promptly, and patients should be evaluated to determine a possible cause of the problem. The cause should be treated, if possible, until the problem is resolved or until the patient’s condition is stabilized. Oseni should not be restarted if liver injury is confirmed and no other cause is found. Oseni should be prescribed with caution in patients with liver disease.

**Hypoglycemia.** Insulin and insulin secretagogues can cause hypoglycemia. A lower dose of the insulin or insulin secretagogue may be required to minimize the risk when used in combination with Oseni.

**Macrovascular risk.** No clinical studies have established conclusive evidence of macrovascular risk reduction with Oseni or with any other antidiabetic drug.

**Dosage and Administration:** Alogliptin/pioglitazone (Oseni) is taken once daily with or without food. The tablets should not be split before swallowing. The 25-mg/15-mg tablets are yellow, round, biconvex, and film-coated. The 12.5-mg/30-mg tablets are pale yellow, the 12.5-mg/15-mg tablets are yellow, round, biconvex, and film-coated. The 25-mg/30-mg combination is available in two strengths: alogliptin 12.5 mg/metformin 500 mg and alogliptin 12.5 mg/metformin 1,000 mg.

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**Pharmaceutical Approval Update**

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Pharmaceutical Approval Update

Pomalidomide (Pomalyst) Capsules

Manufacturer: Celgene, Summit, N.J.

Indication: Pomalidomide is indicated for patients with multiple myeloma (MM) who have received at least two therapies including lenalidomide (Revlimid, Celgene) and bortezomib (Velcade, Takeda/Millennium) and have experienced disease progression on or within 60 days of completion of the last therapy. Approval was based on response rates. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Drug Class: Pomalidomide (4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione) is a chemical analogue of thalidomide (Thalomid, Celgene), which is also approved for MM. The molecular weight is 273.24.

Uniqueness of Drug: Like thalidomide, pomalidomide appears to function through multiple pathways to inhibit myeloma cell growth and survival. Compared with thalidomide, pomalidomide has shown enhanced immunological effects in laboratory testing and is 500 to 2,000 times more potent in stimulating the proliferation of T cells. Pomalidomide appears to combat MM by inhibiting angiogenesis, altering inflammatory and regulatory cytokine levels, and stimulating the immune system cells (T cells and natural killer cells) to destroy myeloma cells.

Boxed Warning: Pomalidomide should not be prescribed for pregnant women because of the risk of life-threatening birth defects. This drug can also cause blood clots resulting from deep vein thrombosis.

Warnings and Precautions:

Embryofetal toxicity. Women of childbearing age should avoid pregnancy for at least 4 weeks after completing therapy. They should either abstain continuously from heterosexual intercourse or use two methods of reliable birth control beginning 4 weeks before starting pomalidomide, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of the therapy. Patients must obtain two negative pregnancy tests before beginning therapy.

Pomalidomide is present in the semen of patients receiving the drug. Men should always use a latex or synthetic condom during any sexual contact with females of reproductive age while taking this drug and for up to 28 days after discontinuing the treatment. Patients must obtain two negative pregnancy tests before beginning therapy.

Blood donations. Patients should not donate blood while they are receiving pomalidomide and for 1 month after they stop treatment in order to prevent any donated blood from being given to a pregnant female patient, whose fetus must not be exposed to this medication.

REMS program. Because of the embryofetal risk, pomalidomide is available only through a Risk Evaluation and Mitigation Strategy (REMS) restricted distribution program called PomaLyst REMS. Prescribers and pharmacists must be certified with the program, and patients must sign an agreement form and comply with the requirements.

Venous thromboembolism. Patients receiving pomalidomide have experienced venous thromboembolic events reported as serious adverse reactions. In the clinical trials, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of deep vein thrombosis or pulmonary embolism was 11%.

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25 mg/45 mg, as appropriate.

For patients switching from alogliptin plus pioglitazone, treatment may be initiated at the dose of each medication based on current therapy. For patients with NYHA Class I or II CHF, the dose is 25 mg/15 mg.

The dose can be titrated up to a maximum of alogliptin 25 mg/pioglitazone 45 mg once daily according to the glycemic response, as determined by glycosylated hemoglobin (HbA1c) levels. After therapy is initiated or if the dose is increased, patients should be carefully monitored for fluid retention (e.g., weight gain, edema, or CHF), which has been noted with pioglitazone.

Renal impairment. For patients with mild renal impairment (a CrCl of 60 mL/minute or greater), no dosage adjustments are necessary.

For those with moderate renal impairment (a CrCl between 30 and 60 mL/minute), the dose is 12.5 mg/15 mg, 12.5 mg/30 mg, or 12.5 mg/45 mg once daily.

Oseni is not recommended for patients with severe renal impairment or end-stage renal disease (a CrCl between 15 and 30 mL/minute) and for end-stage renal disease (a CrCl of less than 15 mL/minute).

The coadministration of pioglitazone and alogliptin 6.25 mg once daily, based on individual requirements, may be considered in these patients. Because dosage adjustments may be necessary depending on renal function, a renal assessment is recommended before therapy is begun and periodically thereafter.

Strong cytochrome P450 2C8 inhibitors. Coadministration of pioglitazone and gemfibrozil (Lopid, Pfizer), a strong CYP2C8 inhibitor, increases pioglitazone exposure by approximately three-fold. Therefore, the maximum recommended dose of Oseni is 25 mg/15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors.

Commentary: The approval of alogliptin was based on data from separate studies for all three formulations. Alogliptin monotherapy (Nesina) was studied in 14 clinical trials involving more than 1,500 patients. Therapy led to additional HbA1c reductions of 0.4 to 0.6 percentage points at 26 weeks.

Alogliptin/metformin (Kazano) was studied in four clinical trials enrolling more than 2,500 patients and produced HbA1c reductions of 1.1 percentage points over alogliptin alone and 0.5 percentage points over metformin at 26 weeks. As with metformin monotherapy, Kazano carries a boxed warning about the risk of lactic acidosis.

Alogliptin/pioglitazone (Oseni) was evaluated in four clinical trials enrolling more than 1,500 patients. Therapy led to additional HbA1c reductions of 0.4 to 0.6 percentage points over pioglitazone alone and 0.4 to 0.9 percentage points over alogliptin alone.

Furiex is entitled to receive royalties and milestones based on sales of alogliptin/pioglitazone (Nesina/Actos). Oseni is considered a replacement for Actos, which lost patent protection in August 2012. Takeda plans to launch Nesina, Kazano, and Oseni in the summer of 2013.

embolism was 3%. Anticoagulation prophylaxis should be considered after an assessment of each patient’s underlying risk factors.

**Hematological toxicities.** Neutropenia of any grade was reported in 50% of patients; it was the most frequently reported grade 3 or 4 adverse event, followed by anemia and thrombocytopenia. Patients should be monitored for hematological toxicities, especially neutropenia, and complete blood counts should be taken weekly for the first 8 weeks and monthly thereafter.

Treatment is continued or modified for grade 3 or 4 hematological toxicities, depending on the clinical and laboratory findings. Dosing interruptions or modifications are recommended to manage neutropenia and thrombocytopenia.

**Hypersensitivity.** Patients with a history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and might be at a higher risk of hypersensitivity reactions.

**Dizziness and confusion.** Eighteen percent of patients experienced dizziness, and 12% of patients experienced confusion; 1% of patients experienced grade 3 or 4 dizziness, and 3% of patients experienced grade 3 or 4 confusion. Patients should be advised to avoid situations that might cause confusion and dizziness, and they should be counseled not to take other medications that might cause these problems without consulting a physician for medical advice.

**Neuropathy.** Eighteen percent of patients experienced neuropathy, with half of these patients experiencing peripheral neuropathy. No cases of grade 3 or higher neuropathic adverse reactions were reported.

**Risk of a second primary malignancy.** Cases of acute myelogenous leukemia have been reported in patients receiving pomalidomide as an investigational therapy apart from MM.

**Dosage and Administration:** The recommended dose for pomalidomide is 4 mg taken orally on days 1 to 21 of repeated 28-day cycles. Cycles are repeated until disease progression.

**Commentary:** According to the National Cancer Institute, multiple myeloma (MM) affects approximately 21,700 Americans yearly (primarily older adults), with half of them dying of the disease. MM is a blood cancer that arises from plasma cells in the bone marrow. In patients with MM, the overgrowth of plasma cells in the bone marrow crowds out normal blood-forming cells, leading to low red blood cell counts and anemia.

The antibody made by the myeloma cells does not fight infections; this is because the myeloma cells are just copies of the same abnormal plasma cell. The antibody can cause kidney damage and even kidney failure.

The approval of pomalidomide was based on a 221-patient clinical trial, in which 7.4% of treated patients had at least partial responses. Additional studies are being conducted to confirm the drug’s clinical benefit and safe use. The FDA granted pomalidomide an accelerated approval and an orphan product designation. A boxed warning mentions the risk of blood clots and life-threatening birth defects if the drug is used in pregnancy.

**Sources:** FDA, February 8, 2013; http://celgene.com; American Cancer Society, www.cancer.org