Pharmaceutical Approval Update

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Iloperidone (Fanapt) Tablets

Manufacturer: Vanda Pharmaceuticals, Rockville, Md.

Indication: Iloperidone tablets are indicated for the acute treatment of adults with schizophrenia; they are not approved for the treatment of patients with dementia-related psychosis.

Drug Class: A mixed dopamine D_2/serotonin 5-HT_{2A} receptor antagonist, iloperidone is an atypical antipsychotic medication.

Uniqueness of Drug: The drug's mechanism of action, like that of other drugs having efficacy in schizophrenia, is unknown; however, it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type-2 (D_2) and serotonin type-2 (5-HT_2) antagonisms. Iloperidone exhibits high-affinity binding to serotonin 5-HT_{2A} and dopamine D_2 and D_3 receptors (Ki values of 5.6, 6.3, 7.1 nM, respectively). Iloperidone has moderate affinity for dopamine D_4, serotonin 5-HT_6 and 5-HT_7, and norepinephrine NEα_1 receptors (Ki values of 25, 43, 22, and 36 nM respectively), and low affinity for the serotonin 5-HT_{1A}, dopamine D_1, and histamine H_1 receptors (Ki values of 168, 216, and 473 nM, respectively). Iloperidone has no appreciable affinity (Ki > 1,000 nM) for cholinergic muscarinic receptors, and it functions as an antagonist at the dopamine D_2, D_3, serotonin 5-HT_{1A}, and norepinephrine alpha$_1$ and alpha$_{2C}$ receptors.

Boxed Warning:

Increased mortality in elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis who are treated with antipsychotic drugs are at an increased risk of death. Iloperidone is not indicated for patients with dementia-related psychosis.

Warnings and Precautions:

Increased risks in elderly patients with dementia-related psychosis. An analysis of 17 placebo-controlled trials, largely in patients taking antipsychotic agents, revealed a risk of death in the drug-treated patients of 1.6 to 1.7 times the risk of death in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared with a rate of about 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that conventional antipsychotic drugs, similar to atypical antipsychotic drugs, may increase mortality rates. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug, as opposed to some characteristics of the patients, is not clear.

Increased mortality. Elderly patients with dementia-related psychosis who are being treated with atypical antipsychotic drugs are at an increased risk of death compared with patients taking a placebo.

Cerebrovascular adverse events, including stroke. In placebo-controlled trials, elderly patients with dementia who received risperidone (Risperdal, Janssen), aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka), and olanzapine (Zyprexa, Lilly) had a higher incidence of cerebrovascular accidents and transient ischemic attacks, including fatalities, compared with the incidence in placebo-treated patients.

Prolonged QT interval. In an open-label study in 160 patients with schizophrenia or schizoaffective disorder, iloperidone 12 mg twice daily was associated with a prolonged corrected QT (QTc) interval of 9 milliseconds (msec). The effect of iloperidone on the QT interval was augmented by the presence of cytochrome P450 2D6 or 3A4 metabolic inhibition, namely paroxetine (Paxil, GlaxoSmithKline) 20 mg once daily and ketoconazole (Nizoral, PriCara) 200 mg twice daily, respectively. With metabolic inhibition of both CYP 2D6 and 3A4, iloperidone 12 mg twice daily was associated with a mean QTc increase from baseline (with Fridericia's correction formula) of about 19 msec. This formula takes into account the physiological shortening of the QT interval that occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates. It is mathematically defined as QTcF = QT/CubeRootRR (seconds) and theoretically corrects the QT interval to that which would be observed at a heart rate of 1 cycle/second.

No cases of torsades de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. Iloperidone should not be taken with other drugs that prolong the QTc interval, including Class 1A (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic medications, antipsychotic agents (chlorpromazine, thioridazine), antibiotics (gatifloxacin, moxifloxacin), or any other class of medications that are known to prolong the QTc interval (pentamidine, levomethadyl acetate, methadone). Iloperidone should also be avoided in patients with congenital long QT syndrome and in those with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsades de pointes, sudden death, or both, in association with the use of drugs that prolong the QTc interval. These events may include bradycardia; hypokalemia or hypomagnesemia; the concomitant use of other drugs that prolong the QTc interval; the presence of a congenital prolonged QT interval; recent acute myocardial infarction (MI); or uncompensated heart failure.

Caution is warranted when iloperidone is prescribed for patients who are taking drugs that inhibit the drug's metabolism and for patients with reduced activity of CYP 2D6.

It is recommended that patients who are at risk for significant electrolyte disturbances undergo baseline measurements of serum potassium and magnesium levels and periodic mon-

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itoring. Hypokalemia, hypomagnesemia, or both, may increase the risk of QT interval prolongation and arrhythmia. Iloperidone should not be prescribed for patients with a history of significant cardiovascular illness such as a prolonged QT interval, recent acute MI, uncompensated heart failure, or cardiac arrhythmias. Iloperidone should be discontinued in patients who have persistent QTc interval measurements above 500 msec. If patients taking iloperidone experience symptoms that could indicate cardiac arrhythmias (e.g., dizziness, palpitations, or syncope), further evaluation, including cardiac monitoring, should be initiated.

Neuroleptic malignant syndrome. A potentially fatal symptom complex, neuroleptic malignant syndrome (NMS), has been reported in association with antipsychotic agents. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Patients may also experience elevated creatine phosphokinase levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of NMS is complex. In arriving at a diagnosis, it is important to identify patients in whom the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms. Other considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever (elevated temperature that occurs after a new medication is started), and primary central nervous system (CNS) pathology.

The management of NMS should include immediately discontinuing antipsychotic drugs and other drugs not essential to concurrent therapy, intensive treatment and medical monitoring of symptoms, and therapy for any concomitant serious medical problems. There is no general agreement about specific pharmacological regimens for NMS. If the patient requires antipsychotic drug treatment after recovery from NMS, reintroducing drug therapy should be carefully considered. The patient should be monitored, because recurrences of NMS have been reported.

Tardive dyskinesia. Potentially irreversible, involuntary dyskinetic movements may develop in patients who take antipsychotic drugs. Although the prevalence of this syndrome appears to be highest among the elderly, especially women, it is impossible to predict, at the start of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the antipsychotic agent increase. However, the syndrome sometimes develops even after relatively brief treatment periods at low doses.

There is no known therapy for tardive dyskinesia, although it may remit partially or completely if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress or partially suppress the signs and symptoms of the syndrome and may thus possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of tardive dyskinesia is unknown.

Given these considerations, iloperidone should be prescribed in a way that is likely to minimize the occurrence of tardive dyskinesia. Long-term therapy with antipsychotic agents should generally be reserved for patients with a chronic illness that is known to respond to antipsychotic drugs and for patients when an alternative that would be equally effective but potentially less harmful is not available or appropriate. In patients who do need chronic treatment, the smallest dose and the shortest duration of therapy that produces a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient who is taking iloperidone, discontinuation of the drug should be considered. However, some patients may require treatment with iloperidone despite the presence of the syndrome.

Hyperglycemia and diabetes mellitus. Hyperglycemia has been reported in patients taking atypical antipsychotic drugs, including iloperidone. In some of these cases, hyperglycemia was extreme and was associated with ketoacidosis or hyperosmolar coma or death. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased underlying risk of diabetes mellitus in patients with schizophrenia and by the increasing incidence of diabetes mellitus in the general population. Thus, although the relationship between atypical antipsychotics and hyperglycemia-related adverse events is not completely understood, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in these patients. Because iloperidone was not marketed at the time these studies were performed, it is not known whether iloperidone is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients using atypical antipsychotic agents are not available.

Patients with diabetes who begin taking atypical antipsychotic agents should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes, such as obesity and a family history, who are starting a regimen of atypical antipsychotic drugs should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. All patients taking these agents should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. If symptoms of hyperglycemia occur during treatment with these medications, fasting blood glucose levels should be measured. In some cases, hyperglycemia resolved when the drug was discontinued, although some patients needed to continue antidiabetic treatment even after discontinuing the suspect drug.

Weight gain. Based on the pooled data from the four placebo-controlled, four-week or six-week, fixed-dose or flexible-dose studies, the proportion of patients having a weight gain of 7% or more was 12% for iloperidone 10 to 16 mg/day, 18% for a dose of 20 to 24 mg/day, and 13% for iloperidone (combined doses) versus 4% for placebo. The mean weight change from baseline to endpoint in the short-term studies was –0.1 kg with placebo and 2 kg with iloperidone. In all short-term and long-term studies, the overall mean change from baseline

at the endpoint was 2.1 kg.

Seizures. In short-term, placebo-controlled trials of four to six weeks, seizures occurred in 0.1% of patients receiving iloperidone and in 0.3% of those receiving placebo. As with other antipsychotic agents, iloperidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (e.g., Alzheimer's dementia), which may be more prevalent in patients 65 years of age or older.

Hypotension and syncope. Iloperidone can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope, a reflection of the drug's alpha$_1$-adrenergic antagonist properties. In double-blind, placebo-controlled, short-term studies in which the dose was increased slowly, syncope was reported in 0.4% of treated patients and in 0.2% of placebo patients. Orthostatic hypotension was reported in 5% of patients given 20 to 24 mg/day, in 3% of patients taking 10 to 16 mg/day, and in 1% of patients given placebo. More rapid titration tends to increase the rate of orthostatic hypotension and syncope.

Iloperidone should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, neutropenia, and agranulocytosis. In clinical trials and postmarketing experience, leukopenia and neutropenia were reported to be temporarily related to antipsychotic agents. Agranulocytosis, sometimes fatal, has also been reported. Possible risk factors include a pre-existing low white blood cell (WBC) count and a history of drug-induced leukopenia and neutropenia. Patients with a pre-existing low WBC count or a history of drug-induced leukopenia and neutropenia should undergo complete blood count (CBC) monitoring frequently during the first few months of treatment and should discontinue iloperidone therapy at the first sign of a decline in WBC count in the absence of other causes. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection, and they should be treated promptly if such symptoms or signs occur. Patients with severe neutropenia (i.e., an absolute neutrophil count below 1,000/mm^3) should discontinue iloperidone and should be monitored for the WBC count until recovery.

Hyperprolactinemia. As with other drugs that antagonize dopamine D$_2$ receptors, iloperidone elevates prolactin levels. Hyperprolactinemia may suppress hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both men and women. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if these drugs are prescribed for patients with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with iloperidone. Neither clinical nor epidemiological studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In a short-term, placebo-controlled trial of four weeks, the mean change from baseline to endpoint in plasma prolactin levels for iloperidone 24 mg/day was an increase of 2.6 ng/mL compared with a decrease of 6.3 ng/mL in the placebo group. Elevated plasma prolactin levels were observed in 26% of adults receiving iloperidone and in 12% receiving placebo. In the short-term trials, iloperidone was associated with modest prolactin elevations when compared with greater prolactin elevations observed with some other antipsychotic agents.

In a pooled analysis from clinical studies including longer-term trials, in 3,210 adults taking iloperidone, gynecomastia was reported in two male subjects (0.1%) compared with 0% in placebo-treated patients. Galactorrhea was reported in eight treated females (0.2%) compared with three placebo-treated females (0.5%).

Regulation of body temperature. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised for patients who will be experiencing conditions that can raise core body temperature, such as strenuous exercise, exposure to extreme heat, the use of a concomitant medication with anticholinergic activity, or dehydration.

Dysphagia. Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Iloperidone and other antipsychotic medications should be used cautiously in patients at risk for aspiration pneumonia.

Suicide. The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for iloperidone should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of an overdose.

Priapism. Three cases of priapism were reported in the premarketing program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Iloperidone shares this pharmacological activity.

Cognitive and motor impairment. As with other antipsychotic drugs, iloperidone has the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled trials, somnolence was reported in 11.9% of adults taking iloperidone 10 mg/day or greater and in 5.3% of those treated with placebo. Patients should be cautioned about operating hazardous machinery and driving until they are certain that iloperidone does not affect them adversely.

Dosage and Administration:

Usual dose. Iloperidone must be titrated slowly from a low starting dose to avoid orthostatic hypotension, which can result from its alpha-adrenergic blocking properties. The recommended starting dose is 1 mg twice daily. Increases to reach the target dose range of 6 to 12 mg twice daily may be made with daily dosage adjustments to 2 mg twice daily on the

second day, 4 mg twice daily on the third day, 6 mg twice daily on the fourth day, 8 mg twice daily on the fifth day, 10 mg twice daily on the sixth day, and 12 mg twice daily on the seventh day.

Efficacy was demonstrated in a dose range of 6 to 12 mg twice daily. Physicians should note that iloperidone must be titrated to an effective dose. Thus, control of symptoms may be delayed during the first one to two weeks of treatment, in contrast to other antipsychotic drugs for which similar titration is not required. Some adverse effects associated with iloperidone use are dose-related.

The maximum recommended dose is 12 mg twice daily (24 mg/day); doses above 24 mg/day have not been systematically evaluated in clinical trials.

Special populations. Dosage adjustments are not routinely indicated on the basis of the patient's age, sex, race, or renal impairment status.

Administration with potential CYP 2D6 and 3A4 inhibitors. The iloperidone dose should be reduced by half when it is given along with strong CYP 2D6 inhibitors such as fluoxetine (Prozac, Lilly) or paroxetine or with strong CYP 3A4 inhibitors such as ketoconazole or clarithromycin (Biaxin, Abbott). When the CYP 2D6 or 3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should then be increased to its previous value.

Hepatic impairment: Iloperidone is not recommended for patients with hepatic impairment.

Maintenance treatment. Although it is not clear how long patients should continue taking iloperidone, it is generally recommended that responding patients continue therapy beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of treatment. Although restarting treatment after discontinuation of therapy has not been specifically addressed, the initiation titration schedule should be followed whenever patients interrupt their regimen for more than three days.

Switching from other antipsychotic agents. There are no specific data that address how patients with schizophrenia can be switched from other antipsychotic drugs to iloperidone or how iloperidone can be used with other antipsychotic agents. Although it might be acceptable to stop previous antipsychotic treatment immediately for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

Dosage forms and strengths. Iloperidone tablets are available in strengths of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg.

Commentary: Iloperidone, an atypical antipsychotic drug, had been around for some time before it was fully developed by Vanda Pharmaceuticals. It had been dropped from development a decade ago after initial clinical trial results indicated it was less effective than other schizophrenia medications such as risperidone (Risperdal) and haloperidol (Haldol). The drug was then sold to Vanda.

When deciding among the alternative treatments available for schizophrenia, health care professionals should note that iloperidone is associated with prolongation of the QTc interval. With some other drugs, a prolonged QTc interval is associated with a tendency to cause torsades de pointes–type arrhythmia, a ventricular tachycardia that can result in sudden death. This possibility suggests that other drugs should be tried first. Whether iloperidone will cause torsades de pointes or will increase the rate of sudden death is not known.

Iloperidone must be titrated to an effective dose (unlike other antipsychotic drugs that do not need to be titrated in a similar manner); therefore, control of symptoms may be delayed during the first couple of weeks of treatment. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the acute treatment of schizophrenia.

Iloperidone is associated with low weight gain, few extrapyramidal symptoms, an absence of induction of diabetes, akathisia, and hyperprolactinemia; little sleepiness; and few negative effects on cognition relative to placebo. However, it has been associated with a prolonged QTc interval to an extent similar to that of the anti-schizophrenic drug ziprasidone (Geodon, Pfizer).

Source: www.iloperidone.com

Bromocriptine Mesylate Tablets (Cycloset)

Manufacturer: VeroScience LLC, Tiverton, R.I.

Indication: Bromocriptine mesylate tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus. The drug should not be used to treat type-1 diabetes or diabetic ketoacidosis. Efficacy data in combination with thiazolidinediones are limited, and its efficacy in combination with insulin has not been confirmed.

Drug Class: Bromocriptine mesylate is a dopamine receptor agonist. It is a single enantiomer with an absolute configuration of 5R, 8R, 2′R, 5′S, 11′S, 12′S. This white or slightly colored, fine crystalline powder has a molecular formula of $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ and a molecular weight of 750.72.

Uniqueness of Product: Although the mechanism by which this ergot derivative improves glycemic control is unknown, taking bromocriptine in the morning improves glycemic control without increasing plasma insulin concentrations in patients with type-2 diabetes. A timed-release, once-daily tablet taken in the morning increases circulating concentrations of bromocriptine for four to five hours.

Warnings and Precautions:

Hypotension and syncope. Hypotension, including orthostatic hypotension, can occur, particularly when bromocriptine therapy begins and when the dose is escalated. In a 52-week, randomized clinical trial of 3,070 patients, hypotension was reported in 2.2% of patients who received bromocriptine and in 0.8% of patients receiving placebo. Among bromocriptine patients reporting symptomatic hypotension, 98% were taking at least one blood pressure medication compared with 73% of patients taking such medications in the total study population. In this trial, six bromocriptine patients (0.3%) and two placebo-treated patients (0.2%) reported orthostatic hypotension. All six patients were taking antihypertensive medications.

Hypotension can result in syncope. In this trial, syncope resulting from any cause was reported in 1.6% of bromocriptine patients and in 0.7% of placebo patients. As a precaution, orthostatic vital signs should be assessed before bromocriptine therapy begins and periodically thereafter. During early treatment with bromocriptine, patients should be

advised to make slow postural changes and to avoid situations that could lead to serious injury if syncope were to occur. Prescribers should use caution when patients are taking antihypertensive drugs.

Psychotic disorders. In patients with severe psychotic disorders, a dopamine receptor agonist such as bromocriptine may exacerbate the disorder or may diminish the effectiveness of drugs used to treat the disorder. Therefore, the use of bromocriptine for these patients in not recommended.

Somnolence. Bromocriptine may cause somnolence. In a 52-week, randomized clinical trial, 4.3% of bromocriptine patients and 1.3% of placebo patients reported somnolence as an adverse event. None of these events were reported as serious, and somnolence usually resolved over time. Patients should be made aware of this potential side effect, particularly when they begin therapy with bromocriptine. Patients experiencing somnolence should not drive or operate heavy machinery.

Interaction with dopamine receptor antagonists. Dopamine receptor antagonists, including neuroleptic agents that have dopamine D_2-receptor antagonist properties (e.g. clozapine, olanzapine, ziprasidone), may reduce the effectiveness of bromocriptine, and bromocriptine may reduce the effectiveness of these agents. Bromocriptine has not been studied in patients taking neuroleptic drugs. The concomitant use of bromocriptine and dopamine receptor antagonists, including neuroleptic drugs, is not recommended.

The effectiveness and safety of bromocriptine in patients who are already taking a dopamine receptor agonist for Parkinson's disease, hyperprolactinemia, restless leg syndrome, acromegaly, or another disorder is unknown.

Macrovascular outcomes. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with bromocriptine or any other antidiabetic drug. In a 52-week, randomized clinical trial, bromocriptine was not associated with an increased risk of adverse cardiovascular events.

Dosage and Administration: The recommended dose of a bromocriptine mesylate tablet is 1.6 to 4.8 mg once daily within two hours after waking in the morning. The tablet should be taken with food to help reduce gastrointestinal (GI) adverse effects such as nausea. Patients start with one tablet (0.8 mg) and increase the dose by one tablet each week until they are taking a maximum daily dose of six tablets (4.8 mg) or the maximum tolerated number of tablets (between two and six per day). The 0.8-mg tablets are white and round, imprinted with the letter C on one side and the number 9 on the other side.

Commentary: Unlike the myriad drugs that are used to treat type-2 diabetes, bromocriptine mesylate (Cycloset) represents a new approach. This drug boosts concentrations of dopamine (phenylethylamine), a monoamine neurotransmitter found in the brain. Dopamine is essential for the normal CNS functioning and helps nerve cells communicate by activating five different receptors.

The tablet is taken orally in the morning, within two hours of awakening, and with food. It is not clear how bromocriptine improves glycemic control in humans, but studies in diabetic animals show that boosting dopamine activity at a particular time of day can reset the biological clock to minimize metabolic problems related to diabetes.

In a year-long trial of 3,070 adults with type-2 diabetes, bromocriptine was superior to placebo in improving glycosylated hemoglobin (HbA_{1c}) levels. In that trial, 39% of patients taking bromocriptine, compared with 11% of patients taking placebo, met the HbA_{1c} goal. Patients taking bromocriptine were less likely to have a heart attack or stroke or to die of heart disease. During the trial, 24% of treated patients, compared with 15% of placebo patients, withdrew from the study. GI effects, particularly nausea, were the main reason patients dropped out of the study.

Sources: www.fda.gov; www.vindy.com

Tolvaptan (Samsca)

Manufacturer: Otsuka Pharmaceutical Co., Ltd., Princeton, N.J.

Indication: Tolvaptan is indicated for patients with significant hypervolemic and euvolemic hyponatremia (below 125 mEq/L or less severe, symptomatic hyponatremia that has not been corrected with fluid restriction) and for patients with heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

Drug Class: Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2 receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan's affinity for the V_2 receptor is 29 times greater than for the V_{1a} receptor. When taken orally, tolvaptan 15 to 60 mg antagonizes the effect of vasopressin and causes an increase in urine water excretion, resulting in an increase in free water clearance, a decrease in urine osmolality, and an increase in serum sodium. Urinary excretion of sodium and potassium and plasma potassium concentrations is not changed significantly. Tolvaptan metabolites have no or weak antagonist activity for human V_2 receptors when compared with tolvaptan. Plasma levels of native AVP may increase by an average of 2 to 9 pg/mL with tolvaptan.

Uniqueness of Drug: Tolvaptan induces free water diuresis in patients with hyponatremia. The drug represents a breakthrough in treating hyponatremia because it directly combats elevated AVP levels associated with SIADH, congestive heart failure, and cirrhosis of the liver.

Boxed Warning:

Initiate and re-initiate therapy only in a hospital, and monitor serum sodium. Tolvaptan therapy should be started or should be re-initiated only in a hospital, where serum sodium levels can be closely monitored. Too rapid a correction of hyponatremia, to a level of more than 12 mEq/L in 24 hours, can cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, changes in mood or affect, spastic quadriparesis, seizures, coma, and death. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction may be advisable.

Warnings and Precautions:

Too rapid a correction of serum sodium can cause serious neurological sequelae. Osmotic demyelination syndrome is a risk when hyponatremia (e.g., above 12 mEq/L in 24 hours) is corrected too quickly. For patients with severe

malnutrition, alcoholism, or advanced liver disease, slower rates of correction may be advisable.

In controlled clinical trials, when tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of the treated subjects with a serum sodium level below 130 mEq/L showed an increase in serum sodium greater than 8 mEq/L at approximately eight hours and 2% had an increase above 12 mEq/L at 24 hours. Approximately 1% of the placebo patients with a serum sodium of below 130 mEq/L showed a rise greater than 8 mEq/L at eight hours. No patient experienced a rise greater than 12 mEq/L in 24 hours. Although none of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, such complications have been reported after serum sodium levels were corrected too rapidly.

Patients should be monitored to assess serum sodium concentrations and neurological status, especially during dose initiation and after titration. Patients with SIADH or with very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of sodium levels. If the rise in serum sodium is too rapid, tolvaptan should be discontinued or interrupted, and administration of hypotonic fluid should be considered. Fluid restriction during the first 24 hours of therapy with tolvaptan may increase the likelihood of overly rapid correction of serum sodium and should be avoided.

GI bleeding in patients with cirrhosis. In patients with cirrhosis who received tolvaptan in hyponatremia trials, GI bleeding was reported in six of 63 tolvaptan-treated patients and in one of 57 (2%) placebo-treated patients. Tolvaptan should be used in patients with cirrhosis only when the need to treat outweighs this risk.

Dehydration and hypovolemia. Tolvaptan induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially if potentially volume-depleted patients are receiving diuretics or if the regimen restricts fluids. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% with tolvaptan and 1.5% with placebo. In tolvaptan patients who experience signs or symptoms of hypovolemia, tolvaptan therapy should be interrupted or discontinued and supportive care should address management of vital signs, fluid balance, and electrolytes. Fluid restriction during therapy with tolvaptan may increase the risk of dehydration and hypovolemia. Patients receiving tolvaptan should continue to ingest fluids in response to thirst.

Coadministration with hypertonic saline. No experiences with the concomitant use of tolvaptan and hypertonic saline have been reported. The concomitant use of tolvaptan and hypertonic saline is not recommended.

Dosage and Administration:

Usual dosage in adults. Patients should be in a hospital when they begin or re-initiate treatment so that their therapeutic response can be evaluated. Too rapid correction of hyponatremia can cause osmotic demyelination, which can result in neurological changes, coma, and death.

The usual starting dose of tolvaptan is 15 mg once daily without regard to meals. The dose is increased to 30 mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed, to achieve the desired serum sodium level. During initiation and titration, changes in serum electrolytes and volume should be monitored frequently. Fluid restriction should be avoided during the first 24 hours of therapy. Patients receiving tolvaptan should be advised that they can continue ingesting fluids when they are thirsty.

Drug withdrawal. After patients discontinue tolvaptan, they should be advised to resume fluid restriction, and they should be monitored for changes in serum sodium and volume status.

Special populations. There is no need to adjust dose based on the patient's age, sex, race, or cardiac or hepatic function.

Renal impairment. There is no need to adjust the dose in patients with mild-to-severe renal impairment (creatinine clearance [CrCl], 10 to 79 mL/minute) because there is no increase in exposure to tolvaptan. Tolvaptan has not been evaluated in patients with a CrCl below10 mL/minute or in patients undergoing dialysis. No benefit can be expected in patients who are anuric.

Commentary: Tolvaptan represents an advance in the therapy for hyponatremia; it directly combats elevated AVP associated with SIADH, congestive heart failure, and hepatic cirrhosis. As a selective AVP V_2-receptor blocker, tolvaptan is used to induce free water diuresis in patients with euvolemic or hypervolemic hyponatremia.

Tolvaptan appears to be safe and effective at promoting aquaresis and in raising serum sodium levels in both short-term and long-term studies. It is also effective in treating patients with congestive heart failure exacerbation, but whether it exerts longstanding beneficial effects for this condition is controversial.

Prolonged use of tolvaptan leads to increased endogenous levels of AVP and perhaps overstimulation of V_{1A} receptors. Theoretically, this activation could lead to increased afterload and cardiac myocyte fibrosis, causing progression of congestive heart failure. However, after 52 weeks of tolvaptan therapy, there was no worsening of left ventricular dilation. In addition, tolvaptan is metabolized by the CYP 3A4 system; thus, physicians should be aware of the potential for increased interactions with other medications.

Sources: www.samsca.com; *Ther Clin Risk Manag* 2008; 4(6):1149–1155 ■