Paliperidone (Invega)

Manufacturer: Janssen (J&J), Titusville, NJ

Indication: Paliperidone, an extended-release tablet, is an atypical antipsychotic agent indicated for the treatment of schizophrenia.

Drug Class: This psychotropic agent belongs to the chemical class of benzisoxazole derivatives. It contains a racemic mixture of (+)– and (–)– paliperidone.

The chemical name is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-
3-yl)-1-piperidinyl[ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-
4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is C_{23}H_{27}FN_{4}O_{3} with a molecular weight of 426.49.

Uniqueness of Product: The tablets are available in 3-mg (white), 6-mg (beige), and 9-mg (pink) strengths. OROS technology (Alza Corp.) employs osmotic pressure to deliver paliperidone at a controlled rate.

The delivery system, which resembles a capsule-shaped tablet in appearance, consists of an osmotically active triple-layer core, surrounded by a subcoat and a semipermeable membrane. This core is composed of two layers containing the drug with excipients and a “push” layer containing osmotically active components. The push layer helps release the drug from the delivery system. There are two precision laser-drilled orifices on the drug-layer dome of the tablet.

Each strength of the tablet has a water-dispersible overcoat and print markings in a different color. In an aqueous environment, such as the gastrointestinal (GI) tract, the water-dispersible color overcoat erodes quickly. Water then enters the tablet through the semipermeable membrane, which controls the rate at which water enters the tablet core. The core, in turn, determines the rate of drug delivery.

The hydrophilic polymers of the core become hydrated and swell, creating a gel containing paliperidone. The gel is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during transit within the GI tract and are eliminated in the stool as a tablet shell, along with insoluble core components.

Boxed Warning:

Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis who take atypical antipsychotic drugs are at an increased risk of death compared with those taking placebo. Analyses of 17 placebo-controlled trials (modal duration, 10 weeks) revealed a risk of death in the drug-treated subjects of between 1.6 and 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared with a rate of about 2.6% in the placebo patients. Although the causes of death varied, most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Paliperidone is not approved for patients with dementia-related psychosis.

Warnings:

QT prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc, including Class I A (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (chlorpromazine, thioridazine), anti-biotics (gatifloxacin, moxifloxacin), or any other class of agents known to prolong the QTc interval. Paliperidone 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 the occurrence of torsades de pointes or sudden death in association with the use of drugs that prolong the QTc interval, including:

- bradycardia.
- hypokalemia or hypomagnesemia.
- the concomitant use of other drugs that prolong the QTc interval.
- the presence of congenital prolongation of the QT interval.

Neuroleptic malignant syndrome: This potentially fatal symptom complex has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, cardiac dysrhythmia). Additional signs of the syndrome may include elevated creatine phosphokinase levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with the syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

Tardive dyskinesia: A syndrome of potentially irreversible, involuntary movements may develop in patients who take antipsychotic drugs. The prevalence of the tardive dyskinesia appears to be highest among the elderly, especially women.

It is not possible to truly know whether atypical antipsychotic drugs have less potential to cause tardive dyskinesia than do the older drugs. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase with the duration of treatment and the total cumulative dose. However, the syndrome can also develop after relatively

Dr. Goldenberg is Executive Director of Pharmaceutical and Scientific Services for MMG Associates in Westfield, New Jersey. His e-mail address is mmgpotter@comcast.com.
brief treatment periods at low doses, although this is uncom-
mon.

Long-term treatment with antipsychotic drugs should gen-
erally be reserved for patients with a chronic illness that is
known to respond to these drugs. In patients who do require
chronic treatment, physicians should prescribe the smallest
dose and the shortest duration of treatment that produces a satis-
factory clinical response. The need for continued treatment
should be reassessed periodically.

Hyperglycemia and diabetes mellitus: All atypical anti-
psychotic agents have been reported to cause hyperglycemia.
In some cases, hyperglycemia was extreme and associated
with ketoacidosis or hyperosmolar coma or death. These cases
were usually noted in postmarketing studies, not in clinical
trials. There have been few reports of hyperglycemia or dia-
betes in trial subjects receiving paliperidone.

Assessment of the relationship between the use of atypical
antipsychotic drugs and glucose abnormalities is complicated
by the possibility of an increased background risk of diabetes
mellitus in patients with schizophrenia and the increasing
incidence of diabetes mellitus in the general population. Given
these confounders, the relationship between atypical anti-
psychotic use and hyperglycemia-related adverse events is
not completely understood. However, epidemiological studies
suggest an increased risk of treatment-emergent hyper-
glycemia-related adverse events in patients treated with the
atypical antipsychotic agents. Because paliperidone was not
marketed at the time these studies were performed, it is not
known whether the agent is associated with this increased risk.

Patients with diabetes mellitus who begin a regimen of atyp-
ical antipsychotics should be monitored regularly for worsen-
ing of glucose control. Patients with risk factors for diabetes
(e.g., obesity, family history of diabetes) who are starting treat-
ment with atypical antipsychotics should undergo fasting blood
glucose testing at the beginning of treatment and periodically
during treatment.

All patients taking atypical antipsychotic agents should be
monitored for symptoms of hyperglycemia (e.g., polydipsia,
polyuria, polyphagia, and weakness). Patients who develop
symptoms of hyperglycemia during treatment with atypical
antipsychotic medications should undergo fasting blood glu-
cose testing. In some cases, hyperglycemia has resolved when
the drug was discontinued; however, some patients required
continuation of antidiabetic treatment despite discontinuation
of the suspect drug.

Gastrointestinal effects: Because the paliperidone tablet is
non-deformable and does not appreciably change in the GI
tract, it should not ordinarily be given to patients with pre-
existing severe GI tract narrowing (e.g., esophageal motility
disorders, small-bowel inflammatory disease, short-gut syn-
drome, peritonitis, cystic fibrosis, chronic intestinal pseudo-
obstruction, or Meckel’s diverticulum).

There have been rare reports of obstructive symptoms in
patients with known strictures in association with the ingestion
of drugs in non-deformable, controlled-release formulations.
Because of the controlled-release design of the tablet, paliperi-
done should be used only in patients who can swallow the
tablet whole. A decrease in transit time, as seen with diarrhea,
would be expected to decrease the drug’s bioavailability. An
increase in transit time, as seen with GI neuropathy, diabetic
gastroparesis, or other causes, would be expected to increase
bioavailability. These changes in bioavailability are more likely
when changes in transit time occur in the upper GI tract.

Dosage and Administration: The recommended dose of paliperidone extended-release tablets is 6 mg once daily, taken
in the morning. Titration of the initial dose is not required.
Although it has not been systematically established that doses
above 6 mg have additional benefit, there was a general trend
for greater effects with higher doses. This must be weighed
against the dose-related increase in adverse effects. Thus,
some patients may benefit from higher doses, up to 12 mg/day.
For other patients, a lower dose of 3 mg/day may be sufficient.

Dose increases above 6 mg/day should be made only after
clinical reassessment, and they generally should occur at
intervals of more than five days. When an increase in dose is
indicated, small increments of 3 mg/day are recommended.
The maximum recommended dose is 12 mg/day.

Paliperidone may be taken with or without food.

Renal impairment: Dosing must be individualized accord-
ing to the patient’s renal function status. For patients with
mild renal impairment (a creatinine clearance [CrCl] between
50 and 80 ml/minute), the maximum recommended dose is
6 mg once daily. For patients with moderate-to-severe renal
impairment (a CrCl between 10 and 50 ml/minute), the max-
imum recommended dose of paliperidone is 3 mg once daily.

Hepatic impairment: For patients with mild-to-moderate
hepatic impairment, (Child-Pugh Classification A and B), no
dose adjustment is recommended.

Commentary: Schizophrenia is a chronic and often debili-
tating mental illness that can cause the patient to withdraw
from people and activities and to retreat into a world of delu-
sions. It is a form of psychosis and a symptom of disordered
brain function. In this type of impaired thinking, patients mis-
interpret reality. The illness affects approximately 1% of the
population worldwide. In men, schizophrenia typically emerges
in the teens or 20s. In women, the onset of schizophrenia is typ-
ically in the 20s or early 30s. There is often no cure, but newer
medications continue to make this poorly understood disease
more manageable.

The once-a-day tablet is derived from risperidone (Risperdal,
Janssen), another atypical antipsychotic drug used to treat
schizophrenia, but paliperidone has an additional hydroxyl
group. In clinical studies, paliperidone was more effective than
placebo in relieving schizophrenia symptoms. However, with-
out studies comparing paliperidone with other schizophrenia
drugs, paliperidone has not yet proved superior to existing
drugs.

Sources: www.mayoclinic.com/health/schizophrenia/
ds00196/dsection=1; www.invega.com

Telbivudine (Tyzeka)
Manufacturer: Idenix, Cambridge, MA/Novartis, East
Hanover, NJ

Indication: Telbivudine tablets are indicated for the treat-
ment of chronic hepatitis B in adults with viral replication and
either persistently elevated levels of serum alanine or aspartate
aminotransferases (ALT or AST) or histologically active
disease. This indication is based on virological, serological, bio-

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chemical, and histological responses after one year of therapy in nucleoside-naïve adults with hepatitis B early antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.

**Drug Class:** Telbivudine is a synthetic thymidine nucleoside analogue with activity against the hepatitis B virus (HBV). The chemical name is 1-((2S,4R,5S)-4-hydroxy-5-hydroxy-methyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-D-ribofuranosyl)-5-methyluracil. Telbivudine is the unmodified β-L-enantiomer of the naturally occurring nucleoside, thymidine. Its molecular formula is C_{10}H_{14}N_{2}O_{5} with a molecular weight of 242.23.

**Uniqueness of Drug:** Telbivudine inhibits HBV DNA polymerase. Telbivudine is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine 59-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 59-triphosphate. Incorporation of telbivudine 59-triphosphate into viral DNA causes termination of the DNA chain, thereby inhibiting HBV replication.

Telbivudine blocks 50% of viral DNA of both HBV first-strand synthesis (EC_{50} = 1.3 ± 1.6 mM) and second-strand synthesis (EC_{50} = 0.2 ± 0.2 mM). At concentrations up to 100 mM, telbivudine 59-triphosphate did not inhibit human cellular DNA polymerases α, β, or γ. No appreciable mitochondrial toxicity was observed in HepG2 cells treated with telbivudine at concentrations up to 10 M M.

**Antiviral Activity:** The antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15 and in primary duck hepatocytes infected with duck HBV. The concentration of telbivudine that effectively inhibited 50% of viral DNA synthesis (EC_{50}) in both systems was approximately 0.2 mM.

The anti-HBV activity of telbivudine was additive with adefovir dipivoxil (Hepsera, Gilead) cell culture, and it was not antagonized by the HIV nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (Videx, Bristol-Myers Squibb) and stavudine (Zerit, Bristol-Myers Squibb). Telbivudine is not active against HIV-1 (EC_{50} above 100 mM) and is not antagonistic to the anti-HIV activity of abacavir (Ziagen, GlaxoSmithKline), didanosine, emtricitabine (Emtriva, Gilead), lamivudine (Epivir-HBV, GlaxoSmithKline), stavudine, tenofovir (Viread, Gilead), or zidovudine (formerly AZT; Retrovir, GlaxoSmithKline).

**Boxed Warning:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretroviral agents. Severe acute exacerbations of hepatitis B have been reported in patients who discontinued anti-hepatitis B therapy, including telbivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, anti-hepatitis B therapy may be resumed.

**Warnings:**

**Exacerbations of hepatitis after discontinuation of treatment:** Severe acute exacerbations of hepatitis B have been reported in patients who have anti-hepatitis B therapy. Hepatic function should be monitored closely for several months after discontinuation of therapy. If warranted, anti-hepatitis B therapy may be resumed.

**Skeletal muscle:** Cases of myopathy (persistent unexplained muscle aches and/or muscle weakness with elevated creatine kinase [CK] values) have been reported with telbivudine use several weeks to months after the start of therapy. Myopathy has also been reported with some other drugs in this class. Uncomplicated myalgia has been reported in telbivudine-treated patients. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or muscle weakness.

Among patients with telbivudine-associated myopathy, there has not been a uniform pattern in terms of the degree or timing of CK elevations. In addition, the predisposing factors for the development of myopathy among telbivudine recipients are unknown. Patients should be advised to promptly report unexplained muscle aches or pain, muscle tenderness, or muscle weakness. Telbivudine therapy should be interrupted if myopathy is suspected, and therapy should be discontinued if myopathy is diagnosed.

It is not known whether the risk of myopathy during treatment with drugs in this class is increased with the concurrent administration of other drugs associated with myopathy, such as corticosteroids, chloroquine, hydroxychloroquine, certain HMG-CoA reductase inhibitors (statins), fibrin acid derivatives, penicillamine, zidovudine cyclosporine, erythromycin, niacin, or azole antifungal agents. Physicians considering potential benefits and risks should monitor patients for any signs or symptoms of unexplained muscle problems, particularly during periods of upward dosage titration.

**Precautions:**

**Renal function:** Telbivudine is eliminated primarily by renal excretion; thus, dose interval adjustment is recommended in patients with a creatinine clearance (CrCl) below 50 ml/minute, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis. The coadministration of telbivudine with drugs that affect renal function may alter plasma concentrations of telbivudine or the coadministered drug.

**Resistance to antiviral drugs for hepatitis B:** There are no adequate or well-controlled studies of telbivudine in patients with lamivudine-resistant HBV infection. In cell culture, telbivudine is not active against HBV encoding amino-acid substitutions of M204I or M204V/L180M. Telbivudine retains wild-type phenotypic activity against the lamivudine resistance-associated substitution of rtM204V alone; however, the efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials.

Studies of telbivudine in patients with adefovir-resistant HBV infection are inadequate. HBV encoding the adefovir resistance-associated substitution of rtN236T remains susceptible to telbivudine, whereas HBV encoding an A181V amino-acid substitution showed a three-fold to five-fold reduced susceptibility to telbivudine in cell culture.

**Liver transplant recipients:** The safety and efficacy of telbivudine in liver transplant recipients are unknown. The steady-state pharmacokinetic properties of telbivudine were not altered after multiple-dose administration in combination with cyclosporine. If telbivudine treatment is determined to be necessary for a liver transplant recipient who has received or continued on page 167
is receiving an immunosuppressant agent that may affect renal function (e.g., cyclosporine, tacrolimus), renal function should be monitored both before and during telbivudine therapy.

**Dosage and Administration:**

**Adults and adolescents (16 years of age or older):** The recommended dose of telbivudine for chronic hepatitis B is 600 mg once daily, taken orally, with or without food. The optimal duration of treatment has not been established.

**Renally impaired subjects:** Telbivudine may be used to treat chronic hepatitis B in patients with impaired renal function. No adjustment to the recommended dose of telbivudine is necessary in patients whose CrCl is 50 ml/minute or above. Adjustment of the dose interval is required in patients with CrCl below 50 ml/minute, including those with end-stage renal disease (ESRD) who are receiving hemodialysis. For patients with ESRD, telbivudine should be administered after hemodialysis. Recommendations are as follows:

- CrCl of 50 ml/minute or more: 600 mg once daily
- CrCl of 30–49 ml/minute: 600 mg once every 48 hours
- CrCl below 30 ml/minute (if not requiring dialysis): 600 mg once every 72 hours
- ESRD: 600 mg once every 96 hours

**Hepatically impaired patients:** No dose adjustment is needed.

**Commentary:** Hepatitis B is a serious disease caused by a virus that attacks the liver. HBV can cause lifelong infection, cirrhosis and scarring of the liver, liver cancer, liver failure, and death. Approximately 70,000 Americans are infected with HBV each year. In patients with chronic HBV, telbivudine can suppress the virus and alleviate liver inflammation in a fashion comparable to that of lamivudine, one of five other drugs approved to treat chronic HBV.

Telbivudine is not a cure for hepatitis B, and the long-term treatment benefits of this drug are not known. The drug did not reduce the risk of transmission of HBV to others through sexual contact or blood contamination. It was generally well tolerated, and most adverse events have been mild to moderate.

Some patients who discontinued taking telbivudine experienced a sudden and severe worsening of hepatitis B. All patients who discontinue treatment should be closely monitored for several months. Patients should stop taking telbivudine only after a careful discussion with the prescribing physician. Drugs in the same class as telbivudine can cause lactic acidosis in some patients as well as severe enlargement and accumulation of fat in the liver.

**Sources:** www.tyzeka.com; www.forbes.com/forbeslife/health/feeds/hscout/2006/10/25/hscout535732.html

**Clindamycin Phosphate 1.2% and Tretinoin 0.025% (Ziana) Gel**

**Manufacturer:** Medics, Scottsdale, AZ

**Indication:** The gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

**Drug Class:** The gel combines a lincosamide antibiotic and a retinoid.

**Uniqueness of Drug:** The product contains two active ingredients. Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic, produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

**Warnings and Precautions:**

**Colitis:** Clindamycin can cause severe colitis, which may result in death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of clindamycin. The gel should be discontinued if significant diarrhea occurs.

**Ultraviolet Light and Environmental Exposure:** Patients should avoid exposure to sunlight and sunlamps and should wear sunscreen daily.

**Contraindications:** The gel is contraindicated in patients with regional enteritis, ulcerative colitis, or a history of antibiotic-associated colitis.

**Dosage and Administration:** Each gram of the product contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 0.25 mg (0.025%) tretinoin in an aqueous-based gel.

At bedtime, the patient should squeeze a pea-sized amount of medication onto one fingertip, dot onto the chin, cheeks, nose, and forehead, then gently rub over the entire face. The gel should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes. The gel is not indicated for oral, ophthalmic, or intravaginal use.

**Commentary:** Acne is a common, recurring disease. Treatment can be complex, often requiring aggressive combination therapy of oral antibiotics and medication applied directly to the skin. Sometimes a long-term strategy is also necessary.

Patients who first received an oral antibiotic and topical gel for acne were often able to maintain their clearer skin by using topical agents alone. Because acne can return after successful treatment, maintenance therapy may be necessary. However, because of a reduced sensitivity of acne to some antibiotics, it has been recommended that antibiotic use be limited to three months. Topical retinoids, medications derived from vitamin A, have been identified as a choice for maintenance therapy.

Three 12-week clinical studies showed that the combination gel was more effective than clindamycin or tretinoin alone for achieving “clear” or “almost clear” status: 21% with Ziana, 16% with clindamycin, 14% with tretinoin, and 8% with the vehicle (the alcohol-free aqueous-based gel) alone.

The combination gel was more effective in reducing inflammatory lesion counts: 48% with Ziana, 42% with clindamycin, 39% with tretinoin, and 26% with the vehicle alone. Ziana also reduced non-inflammatory lesion counts from the baseline evaluation: 36% with Ziana; with clindamycin, 31% with tretinoin, and 16% with placebo (the vehicle gel).

Another study, involving 2,010 patients, further confirmed the improved efficacy of clindamycin/tretinoin gel over clindamycin for (1) achieving clear or almost clear status (41% with Ziana, 34% with clindamycin); (2) decreasing inflammatory lesion counts (61% with Ziana, 58% with clindamycin); and (3) decreasing non-inflammatory lesion counts from baseline (50% with Ziana, 41% with clindamycin).

The major caveat with Ziana is that longer-term clinical studies are needed to determine the possibility of the development of resistance.

**Sources:** www.medicis.com; www.radiology.medscape.com/viewarticle/548709