Sitagliptin/Metformin HCl Tablets (Janumet)

Manufacturer: Merck, Inc., Whitehouse Station, NJ

Indication: Sitagliptin/metformin HCl tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type-2 diabetes mellitus when glucose levels are not adequately controlled with metformin (Glucophage, Bristol-Myers Squibb) or sitagliptin (Januvia, Merck) alone or in patients who are already using a sitagliptin/metformin combination.

Limitation of Use: These tablets should not be used in patients with type-1 diabetes or diabetic ketoacidosis.

Drug Class: The tablets contain two oral antihyperglycemic drugs:

1. Sitagliptin is an orally active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. It is present in the form of sitagliptin phosphate monohydrate, which is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-[(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate.

2. Metformin HCl (N,N-dimethylimidodicarbonimidic diamide HCl) is a member of the biguanide class. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

Uniqueness of Drug: The two antihyperglycemic agents have complementary mechanisms of action.

Sitagliptin is believed to slow the inactivation of incretin hormones; it increases the concentration of the active intact hormones, thereby increasing and prolonging their action. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4.

The incretins are part of an endogenous system involved in the physiological regulation of glucose homeostasis. When blood glucose levels are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic adenosine monophosphate (cAMP). GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Metformin improves glucose tolerance by lowering both basal and postprandial plasma glucose levels. Its pharmacological mechanisms of action differ from those of other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike the sulfonylureas, metformin does not produce hypoglycemia in patients with type-2 diabetes or in normal subjects (except in special circumstances) and does not cause hyperinsulinemia. Insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Black-Box Warning: Lactic acidosis is a rare but serious complication that can result from the accumulation of metformin. The risk increases with sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and abdominal distress. Laboratory abnormalities include low pH, an increased anion gap, and elevated blood lactate levels. If acidosis is suspected, sitagliptin/metformin HCl tablets should be discontinued and the patient should be hospitalized immediately.

Warnings and Precautions:

Lactic acidosis. Lactic acidosis can occur from metformin accumulation during treatment with sitagliptin/metformin HCl tablets, and it is fatal in approximately 50% of cases. It may also occur in association with some pathophysiological conditions (diabetes mellitus) and whenever there is significant tissue hypoperfusion and hypoxemia.

Lactic acidosis is characterized by elevated blood lactate levels (above 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels above 5 mcg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin is very low (0.03 cases per 1,000 patient-years, or 0.015 fatal cases per 1,000 patient-years).

In more than 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical–surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacological management, especially those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at an increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient’s age. The risk, therefore, may be decreased by regular monitoring of renal function in patients tak-
ing metformin, especially older patients, and by using the minimum effective dose of metformin.

Metformin therapy should not be initiated in patients who are 80 years of age and older unless the creatinine clearance (CrCl) demonstrates that renal function is not reduced, because these patients are more susceptible to developing lactic acidosis.

Metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

Because impaired hepatic function may limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake; alcohol potentiates the effects of metformin on lactate metabolism.

Metformin should be temporarily discontinued before any intravascular radiolodine contrast studies and before surgical procedures.

The onset of lactic acidosis may be subtle, accompanied only by nonspecific symptoms (malaise, myalgias, respiratory distress, somnolence, abdominal distress). There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients and their physicians must be aware of the possible importance of such symptoms. Patients should be instructed to notify their physicians immediately if symptoms occur. Metformin should be withdrawn until the problem has been identified.

Determination of serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and even blood metformin levels may be useful. After the patient is stabilized on any dose level of metformin, gastrointestinal (GI) symptoms, which are common during initiation of therapy, are unlikely to be drug-related. GI symptoms that occur later can result from lactic acidosis or another serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal (ULN) but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis; they may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in handling samples.

Lactic acidosis should be suspected in diabetic patients with metabolic acidosis who lack evidence of ketoacidosis (i.e., ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital. If the patient has been taking metformin, the drug should be discontinued immediately and general supportive measures should be instituted promptly. Because metformin is dialyzable (with a clearance of up to 170 mL/minute under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and to remove the accumulated metformin. Such management often results in a prompt reversal of symptoms and in recovery.

**Impaired hepatic function.** Impaired hepatic function has been associated with some cases of lactic acidosis. In general, sitagliptin/metformin should be avoided in patients with evidence of hepatic disease.

**Assessment of renal function.** Metformin and sitagliptin are substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the ULN for their age should not receive sitagliptin/metformin. In the elderly, careful titration is needed to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function.

Before therapy is initiated and at least annually thereafter, renal function should be assessed and verified as normal. If renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and the tablets should be discontinued if renal impairment is evident.

**Vitamin B₁₂ Levels.** In controlled clinical trials of metformin of 29 weeks’ duration, 7% of patients experienced a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels without clinical manifestations. Such a decrease, possibly caused by interference with vitamin B₁₂ absorption from the B₁₂ intrinsic factor complex, however, is rarely associated with anemia, and it appears to be rapidly reversible when metformin is discontinued or if vitamin B₁₂ supplementation is provided.

Annual measurements of hematological parameters are advised in patients taking sitagliptin/metformin. Any apparent abnormalities should be appropriately investigated and managed. Patients with inadequate vitamin B₁₂ or calcium intake or absorption tend to experience subnormal vitamin B₁₂ levels. Routine serum vitamin B₁₂ measurements at two- to three-year intervals may be useful for these patients.

**Alcohol intake.** Because alcohol potentiates the effect of metformin on lactate metabolism, patients should be warned against excessive alcohol intake while taking sitagliptin/metformin HCl tablets.

**Surgical procedures.** Sitagliptin/metformin HCl therapy should be temporarily suspended before surgery except for minor procedures that are not associated with restricted intake of food and fluids. The tablets should not be restarted until the patient’s oral intake has resumed and renal function is judged to be normal.

**Change in clinical status of patients with previously controlled type-2 diabetes.** If patients whose type-2 diabetes has been well controlled with sitagliptin/metformin HCl therapy exhibit laboratory abnormalities or clinical illness (especially vague and poorly defined illness), they should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels should be determined. If either ketoacidosis or lactic acidosis occurs, the tablets must be stopped immediately and other corrective measures initiated.

**Use of Janumet with medications known to cause hypoglycemia:**

**Sitagliptin.** In clinical trials of sitagliptin as monotherapy and with sitagliptin as part of combination therapy with metformin or pioglitazone (Actos, Takeda/Lilly), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. The use of sitagliptin in combination with medications known to cause hypoglycemia, such as the sulfonylureas or insulin, has not been adequately studied.

**Metformin.** Hypoglycemia does not usually occur in
patients receiving metformin alone, but it can occur when caloric intake is deficient, when patients do not compensate for strenuous exercise with caloric supplementation, or during concomitant use with other glucose-lowering agents (e.g., sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in older patients and in patients taking beta-adrenergic blocking drugs.

Concomitant medications affecting renal function or metformin disposition: Caution should be used with concomitant drugs that can affect renal function, that can cause significant hemodynamic changes, or that can interfere with the disposition of metformin (e.g., cationic drugs eliminated by renal tubular secretion).

Radiological studies with contrast materials. Intra-vascular contrast studies with iodinated materials, such as IV urograms, IV cholangiography, angiography, and computed tomography scans with intravascular contrast, can lead to acute alterations in renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, when these studies are planned, sitagliptin/metformin HCl tablets should be temporarily discontinued at the time of or before the procedure, and they should be withheld for 48 hours after the procedure. They should be re-instituted only after renal function has been re-evaluated and has been found to be normal.

Hypoxic states. Cardiovascular collapse (shock) from any cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. If such events occur in patients taking sitagliptin/metformin, the drug should be promptly discontinued.

Loss of glycemic control. When patients who have been stabilized on any diabetic regimen are exposed to stress (fever, trauma, infection, or surgery), glycemic control may be lost temporarily. It may be necessary to withhold sitagliptin/metformin tablets and administer insulin for a while. The tablets may be re-instituted after the acute episode is resolved.

Dosage and Administration. The dosage of antihyperglycemic therapy should be individualized on the basis of the patient’s current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of sitagliptin 100 mg and metformin 2,000 mg. The tablets should generally be given twice daily with meals, with gradual dose escalation, to reduce GI side effects resulting from metformin. The following doses are available: sitagliptin 50 mg/metformin 500 mg and sitagliptin 50 mg/metformin 1,000 mg.

Inadequate glycemic control with metformin monotherapy: If glucose control is inadequate with metformin alone, the usual starting dose should be equal to sitagliptin 100 mg daily (or 50 mg twice daily) plus the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose is sitagliptin 50 mg/metformin 1,000 mg twice daily.

Inadequate glycemic control with sitagliptin monotherapy: If glucose is not adequately controlled with sitagliptin alone, the usual starting dose is sitagliptin 50 mg/metformin 500 mg twice daily. Doses may be titrated up to sitagliptin 50 mg/metformin 1,000 mg twice daily. If patients are taking sitagliptin monotherapy and the dose is adjusted for renal insufficiency, they should not be switched to sitagliptin/metformin tablets.

Switching from sitagliptin/metformin: For patients switching from sitagliptin coadministered with metformin, the combination tablets may be initiated at the dose of sitagliptin and metformin already being taken. No studies have specifically focused on patients who had been previously treated with other oral antihyperglycemic agents and who were then switched to sitagliptin/metformin tablets. Any changes in therapy for type-2 diabetes should be undertaken with care and appropriate monitoring, because glycemic control can be affected.

Commentary: Type-2 diabetes is characterized by elevated blood glucose levels and a lack of proper production of insulin. In the U.S., nearly 21 million people have diabetes, and type-2 accounts for 90% to 95% of cases.

Sitagliptin/metformin HCl tablets were approved as an adjunct to diet and exercise to improve glucose control in type-2 diabetic adults whose glucose levels were not adequately controlled with metformin or sitagliptin alone or in patients already using the combination. The tablets target the three key defects of type-2 diabetes for improved glycemic control: diminished insulin release, uncontrolled production of glucose, and insulin resistance. Sitagliptin addresses diminished insulin release and uncontrolled production of glucose. Metformin addresses insulin resistance and improves insulin sensitivity by increasing glucose uptake and utilization by muscles and tissues. The tablets lower glycosylated hemoglobin values by reducing both postprandial and fasting glucose levels.

Source: www.merck.com/product/usa/pi_circulars/janumet/janumet_pi.pdf

Lapatinib (Tykerb)

Manufacturer: GlaxoSmithKline, Research Triangle Park, NC

Indication: Lapatinib is indicated in combination with capecitabine (Xeloda, Roche) for patients with advanced or metastatic breast cancer whose tumors overexpress a marker called human epidermal receptor type-2 (HER-2) and who have received prior therapy, including an anthracycline, a taxane, and trastuzumab (Herceptin, Genentech).

Drug Class: Lapatinib is a small-molecule agent and a member of the 4-anilinoquinazoline class of kinase inhibitors. It is present as the monohydrate of the ditosylate salt. Its chemical name is N-(3-chloro-4-[(3-fluorophenyl)methyl]oxy)phenyl)-6-[5-[(2-(methylsulfonyl)ethyl)amino]methyl]-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. The molecular formula is C29H26ClFN4O4S(CH3O)2S2H2O.

Uniqueness of Product: Lapatinib inhibits the intracellular tyrosine kinase domains of both epithelial growth factor receptor (EGFR [ErbB-1]) and human epidermal receptor type 2 (HER2 [ErbB-2]) receptors, with estimated apparent kinase (Ki) values of 3 nM and 13 nM, respectively. Its dissociation half-life is 300 minutes or greater. Lapatinib
inhibits ErbB-driven tumor cell growth in vitro and in various animal models.

An additive effect was demonstrated in an in vitro study. Lapatinib and 5-fluorouracil (5-FU), the active metabolite of capecitabine, were used in combination in the four tumor cell lines tested. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing media in vitro. These findings suggest no cross-resistance between these two agents.

**Warnings and Precautions:**

**Decreased left ventricular ejection fraction.** Lapatinib may decrease left ventricular ejection fraction (LVEF). In the randomized clinical trial, most of the decreases in LVEF (more than 60%) occurred within the first nine weeks of treatment; however, data on long-term exposure are limited.

Caution should be exercised in patients with conditions that might impair LV function. LVEF should be evaluated in all patients before lapatinib treatment is begun to ensure that the baseline LVEF is within the institution’s normal limits. The LVEF should continue to be evaluated during treatment to ensure that it does not fall below normal limits.

**Severe hepatic impairment.** For patients with severe hepatic impairment, a dose reduction should be considered.

**Diarrhea.** Diarrhea, sometimes severe, has been reported during treatment with lapatinib. Proactive management with antidiarrheal agents is important. In severe cases, oral or IV electrolytes and fluids may be needed and therapy may have to be interrupted or discontinued.

**QT prolongation.** QT prolongation, as measured by the automated machine-read evaluation of electrocardiograms (ECGs), was observed in an uncontrolled, open-label, dose-escalation study of lapatinib in patients with advanced cancer. Lapatinib should be administered with caution in patients who have or who may develop a prolonged corrected QT (QTc) interval, including patients with hypokalemia or hypomagnesemia, those with congenital long-QT syndrome, patients taking antiarrhythmic agents or other products leading to QT prolongation, and patients receiving cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected before lapatinib administration. Prescribers should consider baseline and on-treatment ECGs with QT measurements.

**Pregnancy.** As a Pregnancy Category D agent, lapatinib can cause fetal harm when given during pregnancy. In one study, pregnant rats were given lapatinib 120 mg/kg per day during organogenesis and through lactation. This dose is approximately 6.4 times the human clinical exposure, based on area-under-the-curve (AUC) concentration. By the fourth day after birth, 91% of the pups had died; of the pups that were given 60 mg/kg per day, 34% were dead. The highest dose that had no effect was 20 mg/kg per day (approximately equal to the human clinical exposure based on AUC concentration).

Lapatinib was studied for its effects on embryofetal development in pregnant rats and rabbits that were given oral doses of 30, 60, and 120 mg/kg per day. There were no teratogenic effects, but minor anomalies (i.e., left-sided umbilical artery, cervical rib, and precocious ossification) occurred in the rats at the maternally toxic dose of 120 mg/kg per day.

In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg per day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC concentration). The drug was also associated with abortions at doses of 120 mg/kg per day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

No adequate or well-controlled studies with lapatinib have been conducted in pregnant women. Women should be advised not to become pregnant when taking lapatinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus.

**Dosage and Administration:** The recommended dose of lapatinib is 1,250 mg (five tablets) orally once daily on days one to 21 continuously in combination with capecitabine 2,000 mg/m² per day (orally in two doses approximately 12 hours apart) on days one to 14 in a repeating 21-day cycle. Lapatinib should be taken at least one hour before or one hour after a meal. Dividing the once-daily dose is not recommended.

Capecitabine should be taken with food or within 30 minutes after food is eaten. If a day’s dose is missed, the dose should not be doubled the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

**Commentary:** The presence of the HER-2 marker in cancerous tissue signals a cancer that is usually more aggressive than the typical breast cancer. The marker is present in approximately 20% of the estimated 178,480 invasive breast cancers that are expected to be diagnosed in women in the U.S. in 2007. This form of breast cancer usually occurs in younger patients. Trastuzumab, which targets this abnormality in breast cancer tissue, has improved response rates and lengthened survival time for many women. It has not always been a cure, but it is a major step forward.

In patients who are unresponsive to trastuzumab, lapatinib in combination with capecitabine is now available for patients with advanced or metastatic breast cancer whose tumors over-express HER-2 and who have received prior therapy, including an anthracycline, a taxane, and trastuzumab. It is the first targeted once-daily oral treatment option for these patients and represents a significant breakthrough for women with advanced HER-2 (ErbB-2)-positive breast cancer. Lapatinib inhibits two validated targets in oncology, the kinase components of the EGFR (ErbB-1) and HER-2 (ErbB-2) receptors, commonly associated with cancer cell proliferation and tumor growth.

This agent, when combined with capecitabine, can be effective for disease that has progressed despite previous therapies. The approval of Tykerb reflects more than 60 clinical trials and investigator-initiated collaborative research studies.

**Source:** www.fda.gov/cder/foi/label/2007/022059lbl.pdf

**Protein C Concentrate (Human) Lyophilized Powder for Solution for Injection (Ceprotin)**

**Manufacturer:** Baxter Healthcare Corporation, Westlake Village, CA

**Indication:** Human protein C concentrate is indicated for
patients with severe congenital protein C deficiency to prevent and treat venous thrombosis and purpura fulminans. It is indicated as a replacement therapy for pediatric and adult patients.

**Drug Class:** Protein C is the precursor of a vitamin K–dependent anticoagulant glycoprotein (serine protease), which is synthesized in the liver. The protein C pathway provides a natural mechanism for control of the coagulation system and for prevention of excessive procoagulant responses to activating stimuli. A complete absence of protein C is incompatible with life.

The concentrate is made from human plasma that has been purified by a combination of filtration and chromatographic procedures, including a column of immobilized mouse monoclonal antibodies on gel beads.

**Uniqueness of Drug:** The manufacturing process includes steps designed to reduce the risk of viral transmission. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation is collected only at FDA-approved blood establishments and is tested by FDA-licensed serological tests for hepatitis B surface antigen, and for antibodies to human immunodeficiency virus (HIV-1/HIV-2) and hepatitis C virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, plasma pools are tested for the presence of HIV-1 and HCV by FDA-licensed nucleic acid testing, and they must be found to be negative.

**Warnings and Precautions:**

Hypersensitivity and allergic reactions. Because the concentrate may contain traces of mouse protein, heparin, or both, as a result of the manufacturing process, allergic reactions to mouse protein or heparin cannot be ruled out. If hypersensitivity or allergic reactions occur, the injection or infusion should be discontinued. In the event of anaphylactic shock, the current medical standards for treatment must be observed.

Transmission of infectious agents. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating or removing a broad range of viruses during manufacture.

Despite these measures, protein C concentrate may carry a risk of transmitting infectious agents (viruses) and, theoretically, the agent for Creutzfeldt–Jakob disease. Physicians who think that an infection might have been transmitted by the concentrate should call Baxter Healthcare at 1-866-888-2472. Physicians should discuss the risks and benefits of this product with patients.

Some viruses, such as human parvovirus B19 (B19V) and hepatitis A, are particularly difficult to remove or inactivate. B19V has the most serious effects in pregnant women (fetal infection) and immunocompromised individuals. Symptoms of infection include fever, drowsiness, chills, and runny nose, followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and abdominal pain. Dark urine and a yellow complexion are also common symptoms. Patients should be encouraged to consult their physicians if any of these symptoms appear.

Appropriate vaccinations for hepatitis A and B should be considered for patients who have received human plasma-derived protein C regularly or repeatedly.

**Bleeding episodes.** Bleeding episodes have been observed in clinical studies. Although concurrent anticoagulant medications may be responsible for these episodes, it is also possible that the administration of protein C concentrate might have further contributed to these events. The simultaneous administration of the product and tissue-plasminogen activator (t-PA) may further increase the risk of bleeding from t-PA.

Heparin-induced thrombocytopenia. Protein C concentrate contains trace amounts of heparin, which may lead to heparin-induced thrombocytopenia. The platelet count should be determined immediately, and discontinuation of the concentrate should be considered.

**Low-sodium diet and renal impairment.** Patients following a low-sodium diet should be informed that the quantity of sodium in the maximum daily dose of protein C concentrate exceeds 200 mg. Patients with renal impairment should be monitored closely for sodium overload.

**Dosage and Administration:** Treatment should be initiated under the supervision of physicians who have experience in replacement therapy with coagulation factors and inhibitors and if they work in a setting where monitoring of protein C activity is feasible.

The product is administered by IV injection after the powder is reconstituted with Sterile Water for Injection. Allergic-type hypersensitivity reactions are possible.

Table 1 presents the dosing schedule for protein C concen-
trate. The dose, administration, frequency, and duration of treatment depend on the severity of the protein C deficiency and the patient's age, clinical condition, and plasma protein C level. The regimen should be adjusted according to the pharmacokinetic profile of each patient.

Commentary: Severe congenital protein C deficiency results in a hypercoagulable state, leading to an abnormal tendency for blood clotting. This can cause severe, often life-threatening blood clots in small blood vessels that, if left untreated, can result in blindness, severe brain damage, multi-organ failure, and death. The deficiency manifests in children early in life, often in utero or in the first few days of life.

The incidence of severe congenital protein C deficiency is estimated to be one to two for every million births. There are fewer than 20 known cases of severe congenital protein C deficiency in the U.S. The FDA has granted this product orphan drug status.

This is the first FDA-approved therapy for patients with severe congenital protein C deficiency. It is indicated as a replacement therapy for children and adults. The approval helps ensure that this critical therapy will continue to be available to patients.