Peg-interferon alfa-2a (Pegasys®)

**Manufacturer:** Roche, Inc., Nutley, NJ

**Indication:** The drug is used for the treatment of adults with chronic hepatitis C who have never been previously treated with interferon and who have compensated liver disease (a damaged but still functioning liver). The drug is also effective in patients with compensated cirrhosis.

**Drug Class:** Peg-interferon alfa-2a, with a molecular weight (MW) of approximately 60 kD, is a covalent conjugate of recombinant alfa-2a interferon (MW, approximately 20 kD) with a single branched bis-monomethoxy polyethylene glycol chain (MW, approximately 60 kD). The PEG moiety is linked at a single site to the interferon moiety via a stable amide bond to lysine. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted and expressed in *Escherichia coli.*

**Uniqueness of Drug:** Peg-interferon alfa-2a is a pegylated interferon that remains active in the bloodstream longer, and at a more constant level, than standard interferon alfa. With the pegylated form, fewer injections are required. The Food and Drug Administration (FDA) has approved peg-interferon alfa-2a on the basis of three pivotal phase III clinical trials that demonstrated its effectiveness in patients with chronic hepatitis C, including cirrhotic patients with compensated liver disease.

**Precautions:** A “black box” warning for alpha interferons, including peg-interferon alfa-2a, states that they may cause or exacerbate life-threatening or fatal neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be closely monitored with periodic clinical and laboratory evaluations. For patients with persistently severe or worsening signs or symptoms of these conditions, therapy should be discontinued. In many cases, these disorders resolve after peg-interferon alfa-2a is withdrawn. Patients with and without previous psychiatric illness should be monitored for such serious or potentially life-threatening conditions as depression, suicidal ideation, and suicidal attempts.

Peg-interferon alfa-2a should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include relapse of drug addiction, drug overdose, aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted.

Peg-interferon alfa-2 suppresses bone marrow function and may result in severe cytopenia. Very rarely, alpha interferons may be associated with aplastic anemia. The manufacturer advises that a complete blood count (CBC) be obtained before treatment and monitored routinely during therapy.

Peg-interferon alfa-2a should be used with caution in patients with baseline neutrophil counts below 1,500 cells/mm³, baseline platelet counts below 90,000 cells/mm³, or baseline hemoglobin levels below 10 g/dl. Peg-interferon alfa-2a therapy should be discontinued, at least temporarily, if severe decreases in neutrophil or platelet counts occur.

Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients who have been treated with peg-interferon alfa-2a. The drug should be administered with caution to patients with pre-existing cardiac disease. Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction occurs, therapy with peg-interferon alfa-2a should be discontinued and appropriate medical therapy should be instituted immediately.

Peg-interferon alfa-2a can cause or aggravate hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been known to develop in patients treated with peg-interferon alfa-2a. Patients with these conditions at the baseline who cannot be effectively treated by medication should not begin peg-interferon alfa-2a therapy. If these conditions develop during treatment and cannot be controlled with medication, therapy may need to be discontinued. Development or exacerbation of autoimmune disorders (e.g., myositis, hepatitis immune thrombocytopenic purpura, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus) have been reported in patients receiving alpha interferon. Peg-interferon alfa-2a should be used with caution in patients with autoimmune disorders.

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, and sarcoidosis, sometimes resulting in respiratory failure or death, may be induced or exacerbated by peg-interferon alfa-2a or by alpha interferon therapy. If persistent or unexplained pulmonary infiltrates or pulmonary impairment develops, treatment should be discontinued. Hemorrhagic or ischemic colitis, sometimes fatal, has been observed within 12 weeks of initiation of alpha interferon treatment. Peg-interferon alfa-2a should be discontinued immediately if the patient experiences abdominal pain, bloody diarrhea, and fever—the typical manifestations of colitis. The colitis usually resolves within one to three weeks of discontinuation of alpha interferon therapy.

Ulcerative colitis has also been seen in patients receiving alpha interferon. Pancreatitis, sometimes fatal, has occurred during alpha interferon treatment. Peg-interferon alfa-2a therapy should be suspended if symptoms or signs suggestive of pancreatitis are observed, and it should be discontinued if a diagnosis of pancreatitis is confirmed.

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Treatment with peg-interferon alfa-2a or other alpha interferons can induce or exacerbate a decrease in or a loss of vision; retinopathy, including macular edema, retinal artery or retinal vein thrombosis, retinal hemorrhages, and cotton-wool spots; optic neuritis; and papilledema. All patients should receive a baseline eye examination. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic examinations during alpha interferon treatment. If ocular symptoms develop, patients should receive a prompt and complete eye examination. Peg-interferon alfa-2a treatment should be discontinued if new or worsening ophthalmologic disorders develop.

**Dosage and Administration:** The recommended dose of peg-interferon alfa-2a is 180 mcg (1.0 ml) once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh. There are no safety and efficacy data on treatment for longer than 48 weeks. Discontinuing therapy should be considered after week 12; virological results are available if the patient has not demonstrated a response.

When a dose must be modified because of moderate to severe clinical or laboratory adverse reactions, reducing the initial dose to 135 mcg (0.75 ml) is generally adequate, although it is sometimes necessary to reduce the dose to 90 mcg (0.5 ml).

**P&T Committee Considerations:** More than 170 million people worldwide are infected with the hepatitis C virus (HCV), which progresses to chronic liver disease in most of these patients. Thus, HCV infection is the cause of significant long-term morbidity and mortality. The major concern with HCV infection is the lack of viral clearance during early infection, which may result in chronic hepatitis C, cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

Interferon-alpha and ribavirin are the mainstays of HCV therapy. Peg-interferon alfa-2a represents an alpha interferon that remains active in the bloodstream longer and at a more constant level than standard interferon alfa. Although a combination of peg-interferon alfa-2a and the antiviral ribavirin will eventually prove to be better in the treatment of HCV, peg-interferon alfa-2a should be placed on the formulary to treat HCV infection.

Compared with the unmodified interferon that has been used until now, peg-interferon alfa-2a shows better characteristics in the treatment of chronic hepatitis C. The modified drug has a biological half-life approximately ten times greater than the 8.5-hour half-life of the unmodified drug, which must be injected three times a week; peg-interferon alfa-2a needs to be injected only once a week. An improved response rate is also superior because of the absence of the serum fluctuations that occur with the unmodified drug.

The cost of peg-interferon alfa-2a is $291 per vial. Each vial delivers a single subcutaneous dose of 180 mcg of the drug in a volume of 1 ml.

**Eplerenone Tablets (Inspra™)**

**Manufacturer:** G. D. Searle, Division of Pharmacia, Chicago, IL

**Indications:** Eplerenone is intended for the treatment of hypertension and can be used alone or in combination with other antihypertensive agents.

**Drug Class:** Preg-4-ene-7, 21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, gamma-lactone methyl ester (7α, 11α, 17α) selectively blocks aldosterone, a key component within the renin–angiotensin aldosterone system (RAAS). The RAAS plays an important role in the body’s regulation of the cardiovascular system.

**Uniqueness of Drug:** Eplerenone selectively blocks aldosterone binding at the mineralocorticoid receptor. Aldosterone synthesis, which occurs in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly by other mechanisms. Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone levels, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resultant increased plasma renin activity and aldosterone-circulating concentrations do not overcome the effect of eplerenone on blood pressure.

**Precautions:** The principal risk associated with eplerenone is hyperkalemia, which can cause serious, sometimes fatal, arrhythmias. This risk can be minimized by careful patient selection, avoidance of certain concomitant treatments, and follow-up. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia, including patients who are receiving concomitant angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, until the effect of eplerenone is established.

**Dosage and Administration:** The recommended starting dose is 50 mg of eplerenone, administered once daily. Its full therapeutic effect is apparent within four weeks. For patients with inadequate blood pressure response, the dosage should be increased to 100 mg twice daily. Higher doses are not recommended, because they are no more effective than a 100-mg dose and because they are associated with an increased risk of hyperkalemia. Eplerenone may be used either alone or in combination with other antihypertensive drugs.

**P&T Committee Considerations:** Despite the availability of several key classes of compounds, control of hypertension has remained inadequate. Eplerenone is the first agent designed to selectively block the hormone aldosterone in the treatment of high blood pressure, and it is expected to provide treatment benefits in a broad range of patients. Eplerenone represents an important new treatment option that goes beyond standard therapies in targeting the aldosterone pathway, which contributes to the development and progression of hypertension. Aldosterone is a key component within the RAAS and plays a significant role in regulating the cardiovascular system.

Clinical trials involving approximately 3,000 patients have demonstrated that eplerenone tablets effectively lower high blood pressure, both alone and in combination with other antihypertensive therapies. The drug has been generally well tolerated and should be placed on the formulary for the treatment of hypertension.

Eplerenone tablets have not yet been placed on the market and have not been priced.
Rosiglitazone Maleate and Metformin Hydrochloride Tablets (Avandamet™)

Manufacturer: GlaxoSmithKline, Research Triangle Park, NC

Indication: As an adjunct to diet and exercise, this combination drug is indicated for the treatment of type 2 diabetes.

Drug Class: Rosiglitazone maleate, which acts directly to increase insulin sensitivity and to decrease insulin resistance, a major underlying cause of type 2 diabetes, is used in combination with an effective oral antidiabetic therapeutic agent, metformin HCl, to control blood sugar (glucose).

Uniqueness of Drug: The drug combines two leading diabetes medications in one convenient tablet. This combination of drugs is characterized by two different mechanisms of action and offers the opportunity to help diabetic patients manage type 2 diabetes for a longer period of time and more effectively compared with previous agents.

Precautions: Lactic acidosis is a rare but serious metabolic complication that can occur as a result of metformin accumulation during treatment with the combination of rosiglitazone maleate and metformin HCl. Lactic acidosis is characterized by elevated blood lactate levels (above 5 mmol/ml), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate-to-pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 mcg/ml are generally found. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency.

When lactic acidosis develops, death occurs in 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiological conditions, including diabetes mellitus, and whenever significant tissue hypoperfusion and hypoxemia are present.

Patients with congestive heart failure who require pharmacological management, particularly patients with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and with the patient’s age.

Unless the creatinine clearance demonstrates that renal function is not impaired, treatment with the drug combination should not be initiated in patients older than age 80, because these patients are more susceptible to the development of lactic acidosis. The drug combination should be promptly withheld from patients with any condition associated with hypoxemia, dehydration, or sepsis.

The drug combination should be avoided in patients with evidence of hepatic disease. Patients should be cautioned against excessive intake of alcohol, because alcohol potentiates the effects of metformin HCl on lactate metabolism. The drug combination should be temporarily discontinued before any intravascular radiocontrast study and any surgical procedure.

Once a patient is stabilized on any dose of the drug combination, gastrointestinal symptoms that are common during initiation of therapy are unlikely to be drug-related. Gastrointestinal symptoms that occur later are sometimes a result of lactic acidosis or other serious disease.

Dosage and Administration: The dose of a rosiglitazone maleate/metformin HCl tablet should be based on the patient’s current doses of both of these agents. The dosage with the combination antidiabetic tablet should be individualized according to the effectiveness and tolerability but should not exceed the maximum recommended daily dose of 8 mg of rosiglitazone maleate/2,000 mg of metformin HCl. The combination should be given in divided doses with meals, with the dose gradually escalated. This strategy reduces gastrointestinal side effects (largely caused by metformin) and permits the physician to determine the minimum effective dose for each patient. Sufficient time should be given to assess adequacy of the therapeutic response. The fasting plasma glucose level should be used to determine the therapeutic response to the drug combination.

If glycemic control is not adequate in one to two weeks after an increase in metformin dosage, or if control is not adequate in eight to 12 weeks after an increase in rosiglitazone dosage, dosage titration is recommended.

If glycemic control is inadequate with metformin monotherapy, the usual starting dose of rosiglitazone maleate/metformin HCl is 4 mg of rosiglitazone (total daily dose) plus the dose of metformin HCl already being taken.

If blood glucose levels are inadequately controlled with rosiglitazone monotherapy, the usual starting dose of rosiglitazone maleate/metformin HCl is 1,000 mg of metformin (total daily dose) plus the dose of rosiglitazone already being taken.

When a switch is made to the combination therapy of rosiglitazone maleate plus metformin HCl, the usual starting dose of the combination is the dose of rosiglitazone and metformin already being taken as separate tablets.

If additional glycemic control is needed, the daily dose of rosiglitazone maleate/metformin HCl may be increased by increments of 4 mg of rosiglitazone and/or 500 mg of metformin, up to the maximum recommended total daily dose of 8 mg of rosiglitazone maleate/2,000 mg of metformin HCl.

P&T Committee Considerations: Rosiglitazone maleate targets insulin resistance, an underlying cause of type 2 diabetes, whereas metformin HCl works to reduce the amount of blood sugar (glucose) produced by the liver. The two medications, when used in combination, target core metabolic defects to help achieve better blood glucose control than metformin alone. These properties make this medication an important option for patients with type 2 diabetes.

When blood glucose concentrations are elevated over an extended period, serious complications can result, including cardiovascular disease, kidney damage, and blindness. To reach normal blood glucose concentrations in patients with type 2 diabetes, it may be necessary to use a combination of therapies that treat the disease more effectively. Therefore, it is recommended that rosiglitazone maleate/metformin HCl tablets be placed on the formulary to treat highly resistant type 2 diabetes.

The average wholesale price is not yet available.