Pharmaceutical Approval Update

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Asenapine Sublingual Tablets (Saphris)

Manufacturer: Schering-Plough, Kenilworth, N.J.

Indication: Asenapine, an atypical antipsychotic agent, is indicated for the acute treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

Drug Class: Asenapine is a dibenzo-oxepino pyrrole. Its molecular formula is $C_{17}H_{16}ClNO \bullet C_4H_4O_4$, and the molecular weight is 401.84.

Uniqueness of Drug: As with other drugs having efficacy in schizophrenia and bipolar disorder, the mechanism of action of asenapine is unknown. It has been suggested that its efficacy in schizophrenia is mediated through a combination of antagonist activity at dopamine D_2 and 5-HT_{2A} (serotonin) receptors.

Boxed Warning: Elderly patients with dementia-related psychosis who are being treated with antipsychotic drugs are at an increased risk of death. Asenapine is not approved for the treatment of patients with dementia-related psychosis.

Warnings and Precautions:

Increased mortality: Elderly patients who have dementia-related psychosis and who are using antipsychotic drugs are at an increased risk of death. Asenapine is not approved for these patients.

Cerebrovascular adverse events (including stroke). In placebo-controlled trials with risperidone (Risperdal, Janssen), aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka), and olanzapine (Zyprexa, Lilly) in elderly subjects with dementia, there was a higher incidence of cerebrovascular accidents and transient ischemic attacks, including fatalities, compared with placebo-treated subjects. Asenapine is not indicated for patients with dementia-related psychosis.

Neuroleptic malignant syndrome. A potentially fatal symptom complex, neuroleptic malignant syndrome (NMS), has been reported in association with the administration of antipsychotic drugs, including asenapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability, such as irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Patients may also have elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Arriving at a diagnosis of NMS is challenging. It is important to exclude 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 (CNS) pathology.

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Patients with NMS should immediately stop taking antipsychotic drugs or other drugs not essential to concurrent therapy. Management includes intensive symptomatic treatment, medical monitoring, and therapy for any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological regimens for NMS. If a patient needs antipsychotic therapy after recovery from NMS, reintroducing such therapy should be carefully considered. Patients should be carefully monitored, because recurrences of NMS have been reported.

Tardive dyskinesia. Potentially irreversible, involuntary dyskinetic movements can develop in patients taking antipsychotic drugs. Although tardive dyskinesia (TD) affects the elderly most often, especially women, it is impossible to predict, at the beginning of antipsychotic treatment, which patients are likely to be affected by the TD syndrome. Whether antipsychotic drug products differ in their potential to cause TD is unknown. The risk of TD and the likelihood that it will become irreversible may increase with the duration of treatment and the total cumulative dose. However, TD can sometimes develop after relatively brief treatment periods at low doses. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic therapy itself, however, may suppress the signs and symptoms of TD and thus might mask the underlying process.

The effect of symptomatic suppression on the long-term course of TD is unknown. Asenapine should be prescribed in a manner that is most likely to minimize the occurrence of TD. In general, chronic antipsychotic treatment should be reserved for patients with a chronic illness that responds to antipsychotic drugs and when other equally effective, but potentially less harmful, treatments are not available or appropriate. For patients who need chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. If signs and symptoms of TD appear in patients receiving asenapine, the drug may need to be discontinued. However, some patients may require treatment with asenapine despite the presence of TD.

Hyperglycemia and diabetes mellitus. Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients receiving atypical antipsychotic agents. In clinical trials, the occurrence of any adverse reaction related to glucose metabolism was less than 1% in both asenapine and placebo groups. The relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies that have not included asenapine suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients who used atypical antipsychotic medications.

Diabetic patients who begin atypical antipsychotic therapy should be monitored regularly for worsening of glucose

control. If these patients have risk factors for diabetes (e.g., obesity and a family history), they should undergo fasting blood glucose testing at the beginning of therapy and periodically during treatment. All patients receiving atypical antipsychotic agents should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who experience symptoms of hyperglycemia while taking these drugs should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the product was discontinued, but some patients may need to continue therapy for diabetes even after they stop taking the antipsychotic drug.

Weight gain. In short-term, placebo-controlled trials of patients with schizophrenia, the mean weight gain was 1.1 kg with asenapine and 0.1 kg with placebo. The proportion of patients with an increase of 7% of more in body weight (at the study's endpoint) was 4.9% for asenapine and 2% for placebo.

In short-term, placebo-controlled trials of patients with bipolar mania, the mean weight gain for asenapine patients was 1.3 kg and 0.2 kg for placebo patients. At the study's endpoint, the proportion of patients with an increase of 7% of more in body weight was 5.8% with asenapine and 0.5% with placebo.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with an increase of 7% or more in body weight (at the study's endpoint) was 14.7%.

Orthostatic hypotension, syncope, and other hemodynamic effects. Asenapine may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its alpha$_1$-adrenergic antagonist activity. In short-term schizophrenia trials, syncope was reported in 0.2% of patients receiving therapeutic doses of asenapine 5 mg or 10 mg twice daily, compared with 0.3% of patients treated with placebo.

In short-term bipolar mania trials, syncope was reported in 0.3% of patients treated with therapeutic doses of asenapine 5 mg or 10 mg twice daily, compared with 0% of patients treated with placebo. During clinical trials, including long-term trials without comparison with placebo, syncope was reported in 0.6% of asenapine patients. Four normal volunteers who were treated with intravenous (IV), oral, or sublingual asenapine experienced hypotension, bradycardia, and sinus pauses. These effects resolved spontaneously in three patients, but the fourth subject received external cardiac massage. The risk of this sequence of events might be greater in nonpsychiatric patients than in psychiatric patients, who might be more adapted to certain effects of psychotropic drugs.

Patients should be instructed about nonpharmacological methods of minimizing orthostatic hypotension, such as sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position. Asenapine should be used with caution in the elderly and in those with cardiovascular disease, cerebrovascular disease, or conditions predisposing to hypotension (such as dehydration, hypovolemia, and antihypertensive treatment). Caution is also advised for patients taking other drugs that can induce hypotension, bradycardia, or respiratory or CNS depression. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

Leukopenia, neutropenia, and agranulocytosis. In clinical trials and postmarketing experience, leukopenia and neutropenia have been temporarily related to antipsychotic agents, including asenapine. Agranulocytosis (including fatal cases) has been reported with other agents in this drug class. Possible risk factors for leukopenia and neutropenia include a preexisting low white blood cell (WBC) count and a history of drug-induced leukopenia and neutropenia; such patients should undergo frequent monitoring of the complete blood count (CBC) during the first few months of therapy. Asenapine should be discontinued at the first sign of a drop in the WBC count in the absence of other causative factors.

Patients with neutropenia should be monitored for fever or other symptoms or signs of infection and should be treated promptly if such symptoms or signs occur. Patients with severe neutropenia (an absolute neutrophil count below 1,000/mm^3) should stop taking asenapine and should undergo WBC count assessments until recovery.

QT prolongation. A trial that involved placebo and asenapine 5 mg, 10 mg, 15 mg, and 20 mg twice daily was conducted to evaluate the drug's effects on QT and corrected QT (QTc) intervals in 151 clinically stable patients with schizophrenia. Electrocardiograms (ECGs) were assessed throughout the dosing interval at baseline and at steady state. At these doses, asenapine was associated with increases in the QTc interval ranging from 2 to 5 milliseconds (msec) compared with placebo. None of the asenapine patients experienced QTc increases of 60 msec or more from baseline measurements, and no patients experienced a QTc of 500 msec or more.

ECGs were evaluated at various times during the clinical trials with asenapine 5 or 10 mg twice daily. Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for asenapine and placebo in these short-term studies. There were no reports of torsades de pointes or other adverse reactions associated with delayed ventricular repolarization.

Asenapine should be avoided in combination with other drugs that prolong the QTc interval, including:

- class 1A antiarrhythmic agents such as quinidine and procainamide (e.g., Procanbid, Monarch).
- class 3 antiarrhythmic agents such as amiodarone (Cordarone, Wyeth) and sotalol (e.g., Betapace, Berlex; Sotalex, Sotacor, Bristol-Myers Squibb).
- antipsychotic medications such as ziprasidone (Geodon, Pfizer), chlorpromazine (Thorazine, GlaxoSmithKline), and thioridazine (Mellaril, Novartis).
- antibiotics such as gatifloxacin (Tequin, Bristol-Myers Squibb [discontinued]) and moxifloxacin (Avelox, Bayer).

Asenapine should also be avoided in patients with a history of cardiac arrhythmias or other conditions that might increase the risk of torsades de pointes or sudden death.

Hyperprolactinemia. Like other drugs that antagonize dopamine D$_2$ receptors, asenapine can elevate prolactin levels. This elevation can persist during chronic administration. 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 in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in men and women. In clinical trials, the incidence of adverse events related to abnormal prolactin levels was 0.4% for asenapine and 0% for placebo.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*. This factor is can be important if these drugs are prescribed for patients with previously detected breast cancer. No clinical or epidemiological studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the evidence is too limited to be conclusive.

Seizures. In short-term schizophrenia and bipolar mania trials, seizures were reported in 0% and 0.3% of patients treated with asenapine 5 mg and 10 mg twice daily, respectively, compared with 0% of patients receiving placebo.

During long-term trials that did not include placebo, seizures were reported in 0.3% of patients receiving asenapine. As with other antipsychotic drugs, asenapine should be used with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold, such as Alzheimer's dementia. Conditions that lower this threshold may be more prevalent in patients 65 years of age or older.

Potential for cognitive and motor impairment. Somnolence has been reported with the use of asenapine. This event was usually transient, with the highest incidence reported during the first week of treatment.

In short-term, fixed-dose, placebo-controlled schizophrenia trials, somnolence was reported in 15% of patients receiving asenapine 5 mg twice daily and in 13% of patients receiving asenapine 10 mg twice daily, compared with 7% of placebo patients. In short-term, placebo-controlled trials involving patients with bipolar mania who received therapeutic doses of asenapine (5 to 10 mg twice daily), somnolence was reported in 24% of asenapine patients and in 6% of placebo patients.

During clinical trials, including long-term studies without placebo, somnolence was reported in 18% of patients receiving asenapine. In short-term, placebo-controlled trials, somnolence (including sedation) led to discontinuation of therapy in 0.6% of patients.

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or motor vehicles, until they are reasonably certain that asenapine is not affecting them adversely.

Body temperature regulation. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. In short-term, placebo-controlled trials for both schizophrenia and acute bipolar disorder, the incidence of adverse reactions suggestive of body temperature increases was low (1% or less) and comparable to placebo.

During long-term trials that did not include placebo, the incidence of adverse reactions suggestive of body temperature increases was 1% or less. Appropriate care is advised for patients who might experience conditions that could contribute to an elevated core body temperature, such as strenuous exercise, exposure to extreme heat, taking another drug with anticholinergic activity, or a tendency toward dehydration.

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

Dysphagia. Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. In short-term schizophrenia and bipolar mania trials, dysphagia was reported in 0.2% of patients treated with asenapine at therapeutic doses of 5 to 10 mg twice daily and in none of the placebo patients. During long-term trials that did not include placebo, dysphagia was reported in 0.1% of asenapine patients.

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, especially in those with advanced Alzheimer's dementia. Asenapine is not indicated for patients with dementia-related psychosis, and it should not be used in patients at risk for aspiration pneumonia.

Use with a concomitant illness. Clinical experience with asenapine in patients with certain concomitant systemic illnesses is limited. Asenapine has not been evaluated in patients with a recent history of MI or unstable heart disease. Patients with these diagnoses were excluded from premarketing trials. Because of the risk of orthostatic hypotension with asenapine, caution should be observed in cardiac patients.

Dosage and Administration: Asenapine is available in an immediate-release, sublingual tablet formulation.

Schizophrenia. The recommended starting and target dose of asenapine is 5 mg given twice daily. In controlled trials, there was no apparent added benefit with the higher dose, but the number of adverse reactions was increased. The safety of doses above 10 mg twice daily has not been evaluated. Although it is not clear how long patients with schizophrenia should continue to take asenapine, it is recommended that responding patients continue therapy beyond the acute response.

Bipolar disorder:

Acute treatment: The recommended starting dose of asenapine for adults, and the dose maintained by 90% of the patients studied, is 10 mg twice daily. The dose can be decreased to 5 mg twice daily if there are adverse effects. In controlled trials, the starting dose for asenapine was 10 mg twice daily. On the second and subsequent days of the trials, the dose could be lowered to 5 mg twice daily, based on tolerability, but the dose was reduced in fewer than 10% of patients. The safety of doses above 10 mg twice daily has not been studied.

Maintenance treatment. Although it is not clear how long patients with bipolar disorder should continue to take asenapine, responding patients should continue therapy beyond the acute response.

Instructions: To ensure optimal absorption, patients should place the tablet under the tongue and allow it to dissolve completely (usually within seconds). The tablet should not be crushed, chewed, or swallowed. Patients should be instructed not eat or drink for 10 minutes after administration.

Special populations:

Hepatic impairment. In a study of patients with hepatic impairment who received a single 5-mg dose of asenapine,

increases in asenapine exposures (compared with subjects with normal hepatic function) were correlated with the degree of impairment. Even though no dosage adjustments were required in patients with mild (Child–Pugh A) or moderate (Child–Pugh B) impairment, asenapine levels were increased, on average, by seven-fold in patients with severe hepatic impairment (Child–Pugh C) compared with patients with normal hepatic function. Therefore, asenapine is not recommended for patients with severe hepatic impairment.

Renal impairment. Dosage adjustments are not routinely required on the basis of age, sex, race, or renal impairment status.

Switching from other antipsychotic drugs. No data have specifically addressed switching patients with schizophrenia or bipolar mania from other antipsychotic drugs to asenapine or giving asenapine along with other antipsychotic drugs. Immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, but more gradual discontinuation may be more appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

Commentary: Schizophrenia affects about 24 million people worldwide, including two million Americans; bipolar I disorder affects about 1% of adults, including 10 million Americans. These complex medical conditions can present clinical challenges for physicians, and new treatments may be beneficial in managing patients' symptoms.

The FDA approved asenapine sublingual tablets for the acute treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder, with or without psychotic features, in adults. Asenapine can be used as a first-line treatment, and it is the first psychotropic drug to receive an initial approval for both of these indications simultaneously. Asenapine represents a new choice for patients starting treatment and for those who have discontinued previous treatment.

Asenapine may be comparable in efficacy and safety to other atypical antipsychotics. With Risperdal already available as a generic drug and the other major brand names exected to acquire generic status over the next two years, asenapine might not represent an advantage over existing drugs if it turns out to be more expensive than generic brands. In the fourth quarter of 2009, however, it might be still sold at a lower price than the brands that will be going generic over the next few years.

Sources: www.spfiles.com/pisaphrisv1.pdf; www.saphris.com

Saxagliptin (Onglyza) Tablets

Manufacturer: Bristol-Myers Squibb, Princeton, N.J.

Indication: Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus. It should not be used patients with type-1 diabetes mellitus or diabetic ketoacidosis. Saxagliptin has not been studied in combination with insulin.

Drug Class: Saxagliptin is an orally active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. The molecular weight is 333.43.

Uniqueness of Drug: Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP-4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type-2 diabetes, GLP-1 is reduced, but the insulin response to GLP-1 is preserved.

DPP-4 inhibitors affect the action of natural hormones called incretins. Saxagliptin is a competitive DPP-4 inhibitor that slows the inactivation of the incretins. Incretins decrease blood glucose levels by increasing consumption of glucose by the body, mainly through increasing insulin production in the pancreas and reducing the production of glucose by the liver.

Warnings and Precautions:

Use with medications known to cause hypoglycemia. Because insulin secretagogues (such as the sulfonylureas) cause hypoglycemia, a lower dose may be required to reduce the risk of hypoglycemia when they are used with saxagliptin.

Macrovascular outcomes. No clinical studies have established evidence of a reduced macrovascular risk with saxagliptin or any other antidiabetic drug.

Dosage and Administration: The recommended dose of saxagliptin is 2.5 mg or 5 mg once daily without regard to meals. A dose of 2.5 mg daily is recommended for patients with moderate or severe renal impairment or end-stage renal disease (defined as a creatine clearance of 50 mL/minute or lower). Renal function should be assessed before treatment begins and periodically thereafter.

A dose of 2.5 mg daily is recommended for patients who are also taking strong cytochrome CYP 450 3A4 and 3A5 inhibitors such as the antifungal agent ketoconazole (Nizoral, Janssen).

Commentary: The approval of saxagliptin represents the introduction of another DPP-4 inhibitor on the U.S. market in addition to sitagliptin phosphate (Januvia, Merck). Both drugs cost approximately $5.72 per tablet for common dosages (the U.S. wholesale price), and each of these agents improves the body's ability to reduce elevated blood glucose levels. The DPP-4 inhibitors are a relatively new class of drugs that can be taken along with older diabetes drugs, such as metformin (Glucophage, Bristol-Myers Squibb). The saxagliptin tablet is smaller than sitagliptin, is easier to swallow, and can be taken once daily with metformin, whereas Merck's Janumet (a combination of sitagliptin and metformin) is taken twice daily.

There is some concern that saxagliptin may increase the risk of cardiovascular events for patients who already have heart problems. The FDA is requiring Bristol-Myers Squibb to conduct testing to address this matter. General concerns have been expressed about the potential cardiovascular risks of DPP-4 inhibitors, which is probably why similar drugs by Novartis and Takeda are still not available in the U.S.

The prescribing information for saxagliptin seems to suggest few advantages in efficacy over sitagliptin, and because the manufacturer has matched the price of sitagliptin, there might also be little financial advantage of one agent over the other. However, most physicians prefer to have more than one drug choice in the same class because individual patients respond to medications differently.

Source: http://packageinserts.bms.com/pi/pi_onglyza.pdf

Interferon beta-1b (Extavia) Injection

Manufacturer: Novartis, Florham Park, N.J.

Indication: Interferon beta-1b is indicated for patients with relapsing forms of multiple sclerosis (MS), a chronic autoimmune disease, to reduce the frequency of clinical exacerbations. The product is also intended for those patients who have experienced a first clinical episode and have features consistent with MS on magnetic resonance imaging (MRI).

Drug Class: This purified, sterile, lyophilized protein is produced by recombinant DNA techniques. It is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta Ser17. The native gene is obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17.

Interferon beta-1b has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material. Because this agent contains the same active ingredients as other interferon beta-1b drugs, these products should not be given at the same time.

The medication's specific activity is approximately 32 million IU/mg. Each vial contains 0.3 mg.

Uniqueness of Product: The exact mechanism of action of interferon beta-1b in patients with MS is unknown. However, the drug has inhibitory effects on proliferation of leukocytes and antigen presentation. Interferon beta-1b may also modulate the profile of cytokine production toward that of the anti-inflammatory phenotype, and this appears to occur in the systemic circulation and within the CNS. Interferon beta-1b can also reduce T-cell migration by inhibiting T-cell matrix metalloproteinases. These activities are likely to act in concert to account for the mechanism of interferon beta-1b in MS.

Warnings and Precautions:

Depression and suicide. Interferon beta-1b should be used with caution in patients with depression, which is common in patients with MS. Depression and suicide have occurred in patients receiving interferon compounds, including interferon beta-1b. Patients should be advised to report symptoms of depression or suicidal ideation to their physicians immediately. If depression occurs, patients might need to stop taking interferon beta-1b. In four randomized, controlled studies, there were three suicides and eight suicide attempts among 1,532 patients receiving interferon beta-1b and one suicide and four suicide attempts among 965 placebo patients.

Injection-site necrosis. In controlled clinical trials, injection-site necrosis was reported in 4% of patients. Typically, this event occurs within the first four months of therapy, although it can occur more than one year after initiation of therapy. Necrosis can occur at a single site or at multiple injection sites. The necrotic lesions are typically 3 cm or less in diameter but may be larger. Generally, the necrosis extends only to subcutaneous fat, but it can also include the fascia overlying muscle. In some biopsy results, vasculitis was reported. For some lesions, debridement and skin grafting were required.

As with any open lesion, it is important to avoid infection. If infection occurs, it should be treated. In the trials, the time to healing varied, depending on the severity of the necrosis at the time treatment began. In most cases, healing was associated with scarring. For some patients, necrotic skin lesions healed while therapy continued. Whether to discontinue therapy following a single instance of necrosis depends on the extent of necrosis. For patients who continue therapy after necrosis has occurred, interferon beta-1b should not be injected into the affected area until the area is fully healed. If multiple lesions occur, therapy should be discontinued until healing occurs.

The patient's understanding and use of aseptic self-injection techniques should be periodically re-evaluated, particularly if injection-site necrosis has occurred.

Injection-site reactions. In controlled clinical trials, injection-site reactions occurred in 78% of patients receiving interferon beta-1b, including necrosis, inflammation, pain, hypersensitivity, masses, and edema, as well as nonspecific reactions. The incidence of these reactions tended to decrease over time. Approximately 69% of patients experienced a reaction during the first three months of treatment, and approximately 40% experienced them at the end of the studies.

Anaphylaxis. Anaphylaxis has been reported as a rare complication of interferon beta-1b use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash, and urticaria.

Flu-like symptom complex. In controlled clinical trials, the rate of a flu-like symptom complex was approximately 57%. The incidence decreased over time, with only 10% of patients reporting this event at the end of the studies. The median duration of a flu-like symptom complex in one study was 7.5 days.

Leukopenia. In controlled clinical trials, leukopenia was reported in 18% of treated patients receiving interferon beta-1b, leading to a reduction of the dose in some patients. Monitoring of CBC and differential WBC counts is recommended.

Elevated hepatic enzymes. In clinical trials, elevated alanine transaminase (ALT) levels to more than five times baseline value were reported in 12% of treated patients, and an increase of aspartate transaminase (AST) levels to more than five times the baseline value was reported in 4% of treated patients, resulting in reduced doses or cessation of therapy for some patients. Monitoring of liver function is recommended.

Laboratory tests. In addition to the tests normally required for monitoring patients with MS, CBC and differential WBC counts, platelet counts, and blood chemistry profiles (including liver function tests) and are recommended at regular intervals (at one, three, and six months) following the introduction of interferon beta-1b therapy and then periodically thereafter if there are no clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as indicated. Patients with myelosuppression may require more intensive monitoring of CBC counts, differential WBC counts, and platelet counts.

Human albumin USP. Interferon beta-1b contains albumin, a derivative of human blood. Depending on effective donor screening and product manufacturing processes, albumin can carry a very small risk of transmission of viral diseases. A theoretical risk of transmitting Creutzfeldt–Jakob disease (CJD) is considered remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Contraindications. Patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin USP, or other components of the formulation should not

Table 1 **Dose–Titration Schedule for Extavia**

Recommended Titration		Interferon beta-1b (Dose)	Volume
Weeks 1–2	25%	0.0625 mg	0.25 mL
Weeks 3–4	50%	0.1250 mg	0.50 mL
Weeks 5–6	75%	0.1875 mg	0.75 mL
Week 7+	100%	0.2500 mg	1.00 mL

use interferon-beta-1b.

Dosage and Administration: The recommended dose is 0.25 mg, injected subcutaneously every other day. Generally, patients receive a starting dose of 0.0625 mg (0.25 mL) subcutaneously every other day. The dose is then increased over a six-week period to 0.25 mg (1 mL) every other day (Table 1).

To reconstitute lyophilized interferon beta-1b for injection, the clinician attaches the prefilled syringe containing the diluent (sodium chloride, 0.54% solution) to the interferon beta-1b vial, then slowly injects 1.2 mL of diluent into the vial. The vial is gently swirled until the drug is dissolved completely. The vial should not be shaken. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, the vial should be allowed to sit undisturbed until the foam settles. The clinician should visually inspect the reconstituted product before use and should discard the product if it contains particulate matter or if it is discolored. With the syringe and vial adapter in place, the assembly is turned over so that the vial is on top. The appropriate dose of the solution is withdrawn, and the vial is removed from the vial adapter before interferon beta-1b is injected: 1 mL of reconstituted product solution contains interferon beta-1b 0.25 mg/mL.

Commentary: MS affects approximately 400,000 patients in the U.S. More than 80% of these patients have the relapsing–remitting form. MS is one of the most common causes of neurological disability in young adults, resulting in impaired muscle control and strength, vision, balance, sensation, and mental function.

Interferon beta-1b, which has been shown to reduce annualized relapse rates by 34%, is the first in a new planned portfolio of MS medications from Novartis. The Novartis product is similar to the Bayer's Betaseron and offers patients and physicians a new branded version of a first-line, disease-modifying therapy that has been the standard of care for MS in the U.S. for more than 16 years. Novartis is marketing a "me-too" drug, which might appear unusual in this age of high profits sought by large drug companies for a disease with a small population of patients; however, the company hopes to gain experience in the MS marketplace as it anticipates a future launch of fingolimod (FTY720), the first sphingosine-1-phosphate (S1P) receptor modulator. It is currently in phase 3 clinical trials as a monotherapy for relapsing–remitting MS.

Along with their prescriptions, patients will have access to a support program, including a nurse help line, injection training, reimbursement support services, and an autoinjector from Novartis.

Source: www.pharma.us.novartis.com/product/pi/pdf/extavia.pdf ■