HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Extavia safely and effectively. See full prescribing information for Extavia.

Extavia (Interferon beta-1b) Kit for subcutaneous use
Initial U.S. Approval: 7/23/93

----------INDICATIONS AND USAGE----------

Extavia is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. (1)

----------DOSAGE AND ADMINISTRATION----------

- For subcutaneous use only. (2)
- The recommended dose is 0.25 mg injected subcutaneously every other day. Generally, start at 0.0625 mg (0.25 mL) subcutaneously every other day, and increase over a six week period to 0.25 mg (1 mL) every other day. (2)
- Instruct patients in the use of aseptic technique when administering Extavia. (17.5)

----------DOSAGE FORMS AND STRENGTHS----------

Lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP. (3).

----------CONTRAINDICATIONS----------

History of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Depression and suicide: advise patients to immediately report any symptom of depression and/or suicidal ideation; consider discontinuation of Extavia if depression occurs. (5.1)
- Injection site necrosis: do not administer Extavia into affected area until it is fully healed; if multiple lesions occur, therapy should be discontinued until healing occurs. (5.2)
- Injection site reactions. (5.3)
- Anaphylaxis and other allergic reactions. (5.4)
- Flu-Like Symptom Complex. (5.5)
- Leukopenia: monitor CBC. (5.6, 5.8)
- Liver enzymes abnormalities: monitor liver function tests. (5.7, 5.8)
- Monitor thyroid function tests every 6 months in patients with history of thyroid dysfunction. (5.8)

----------ADVERSE REACTIONS----------

In controlled studies with interferon beta-1b, the most common adverse reactions (at least 2% more than placebo) were: Lymphopenia, neutropenia, leukopenia, lymphadenopathy, headache, insomnia, incoordination, hypertension, dyspnea, abdominal pain, increased liver enzymes, rash, skin disorder, hypertonia, myalgia, urinary urgency, metrorrhagia, impotence, injection site reaction, asthenia, flu-like symptom complex, pain, , fever, chills, peripheral edema, chest pain, malaise, and injection site necrosis (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

No formal drug interaction studies have been conducted. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: use EXTAVIA with caution. (8.3)
- Pediatric Use: Safety and efficacy not established in patients under 18 years of age. (8.3)
- Geriatric Use: Safety and efficacy not established in patients age 65 years or older. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: July 2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXTAVIA (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

The recommended dose of EXTAVIA is 0.25 mg injected subcutaneously every other day.

Generally, patients should be started at 0.0625 mg (0.25 mL) subcutaneously every other day, and increased over a six week period to 0.25 mg (1 mL) every other day (see Table 1).

Table 1. Schedule for Dose Titration

	Recommended Titration	EXTAVIA Dose	Volume
Weeks 1-2	25%	0.0625 mg	0.25 mL
Weeks 3-4	50%	0.125 mg	0.5 mL
Weeks 5-6	75%	0.1875 mg	0.75 mL
Week 7+	100%	0.25 mg	1 mL

To reconstitute lyophilized EXTAVIA for injection, attach the prefilled syringe containing the diluent (Sodium Chloride, 0.54% Solution) to the EXTAVIA vial using the vial adapter. Slowly inject 1.2 mL of diluent into the EXTAVIA vial. Gently swirl the vial to dissolve the drug completely; do not shake. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, allow the vial to sit undisturbed until the foam settles. Visually inspect the reconstituted product before use; discard the product if it contains particulate matter or is discolored. Keeping the syringe and vial adapter in place, turn the assembly over so that the vial is on top. Withdraw the appropriate dose of EXTAVIA solution. Remove the vial from the vial adapter before injecting EXTAVIA. One mL of reconstituted EXTAVIA solution contains 0.25 mg of Interferon beta-1b/mL.

EXTAVIA is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections. Patients should be advised to rotate sites for subcutaneous injections (see Patient Counseling Information 17.5). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. EXTAVIA should be visually inspected for particulate matter and discoloration prior to administration.

3 DOSAGE FORMS AND STRENGTHS

EXTAVIA is supplied as a lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP. Drug is packaged in a clear glass, single-use vial (3 mL capacity). A pre-filled single-use syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution), two alcohol prep pads, and one vial adapter with attached 27 gauge needle are included for each vial of drug. EXTAVIA and the diluent are for single-use only. Unused portions should be discarded. Store at room temperature.

4 CONTRAINDICATIONS

EXTAVIA is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicide

EXTAVIA (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Interferon beta-1b. Patients treated with EXTAVIA should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of EXTAVIA therapy should be considered.

In the four randomized controlled studies there were three suicides and eight suicide attempts among the 1532 patients in the Interferon beta-1b treated groups compared to one suicide and four suicide attempts among the 965 patients in the placebo groups.

5.2 Injection Site Necrosis

Injection site necrosis (ISN) has been reported in 4% of patients in controlled clinical trials *[see Adverse Reactions (6.1)]*. Typically, injection site necrosis occurs within the first four months of therapy, although post-marketing reports have been received of ISN occurring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic lesions are typically three cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat. However, there are also reports of necrosis extending to and including fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions debridement and, infrequently, skin grafting have been required.

As with any open lesion, it is important to avoid infection and, if it occurs, to treat the infection. Time to healing was varied depending on the severity of the necrosis at the time treatment was begun. In most cases healing was associated with scarring.

Some patients have experienced healing of necrotic skin lesions while Interferon beta-1b therapy continued; others have not. Whether to discontinue therapy

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated, particularly if injection site necrosis has occurred.

5.3 Injection Site Reactions

In controlled clinical trials, injection site reactions occurred in 78% of patients receiving Interferon beta-1b with injection site necrosis in 4%. Injection site inflammation (42%), injection site pain (16%), injection site hypersensitivity (4%), injection site necrosis (4%), injection site mass (2%), injection site edema (2%) and non-specific reactions were significantly associated with Interferon beta-1b treatment . The incidence of injection site reactions tended to decrease over time. Approximately 69% of patients experienced the event during the first three months of treatment, compared to approximately 40% at the end of the studies.

5.4 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 *[see Adverse Reactions (6.1)]*.

5.5 Flu-Like Symptom Complex

In controlled clinical trials, the rate of flu-like symptom complex was approximately 57%. The incidence decreased over time, with only 10% of patients reporting flu-like symptom complex at the end of the studies., The median duration of flu-like symptom complex in Study 1 was 7.5 days *[see Clinical Studies (14)]*.

5.6 Leukopenia

In controlled clinical trials, leukopenia was reported in 18% of patients receiving Interferon beta-1b, leading to a reduction of the dose of Interferon beta-1b in some patients [see Adverse Reactions (6.1)]. Monitoring of complete blood and differential white blood cell counts is recommended [see Warnings and Precautions (5.8)].

5.7 Hepatic enzymes elevations

In controlled clinical trials, elevations of SGPT to greater than five times baseline value were reported in 12% of patients receiving Interferon beta-1b, and increase of SGOT to greater than five times baseline value were reported in 4% of patients receiving Interferon beta-1b, leading to dose-reduction or discontinuation of treatment in some patients *[see Adverse Reactions (6.1)]*. Monitoring of liver function tests is recommended *[see Warnings and Precautions (5.8)]*.

5.8 Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of EXTAVIA therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

5.9 Albumin (Human), USP

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

In all studies, the most serious adverse reactions with Interferon beta-1b were depression, suicidal ideation and injection site necrosis (see Warnings and Precautions). The incidence of depression of any severity was approximately 30% in both Interferon beta-1b-treated patients and placebo-treated patients. Anaphylaxis and other allergic reactions have been reported in patients using Interferon beta-1b [*see Warnings and Precautions (5.4)]*. The most commonly reported adverse reactions were lymphopenia (lymphocytes<1500/mm^3), injection site reaction, asthenia, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Interferon beta-1b, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertonia, and myasthenia.

Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of Interferon beta-1b cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Interferon beta-1b in the four placebo controlled trials of 1407 patients with MS treated with 0.25 mg or 0.16 mg/m^2, including 1261 exposed for greater than one year. The population encompassed an age range from 18 – 65 years. Sixty-four percent (64%) of the patients were female. The percentages of Caucasian, Black, Asian, and Hispanic patients were 94.8%, 3.5%, 0.1%, and 0.7%, respectively.

The safety profiles for Interferon beta-1b-treated patients with SPMS and RRMS were similar. Clinical experience with Interferon beta-1b in other populations (patients with cancer, HIV positive patients, etc.) provides additional data regarding adverse reactions; however, experience in non-MS populations may not be fully applicable to the MS population.

Table 2 enumerates adverse events and laboratory abnormalities that occurred among all patients treated with 0.25 mg or 0.16 mg/m^2 Interferon beta-1b every other day for periods of up to three years in the four placebo controlled trials (Study 1-4) at an incidence that was at least 2.0% more than that observed in the placebo patients (System Organ Class, MedDRA v. 8.0).

Table 2 Adverse Reactions and Laboratory Abnormalities

System Organ Class MedDRA v. 8.0 [#] Adverse Reaction	Placebo (n=965)	Interferon beta-1b (n=1407)
Blood and lymphatic system disorders		

Absolute neutrophil count decreased (< 1500/mm^3) [x]	5%	13%
White blood cell count decreased (< 3000/mm^3) [x]	4%	13%
Lymphadenopathy	3%	6%
Nervous system disorders		
Headache	43%	50%
Insomnia	16%	21%
Incoordination	15%	17%
Vascular disorders		
Hypertension	4%	6%
Respiratory, thoracic and mediastinal disorders		
Dyspnea	3%	6%
Gastrointestinal disorders		
Abdominal pain	11%	16%
Hepatobiliary disorders		
Alanine aminotransferase increased(SGPT > 5 times baseline)[x]	4%	12%
Aspartate aminotransferase increased(SGOT > 5 times baseline)[x]	1%	4%
Skin and subcutaneous tissue disorders		
Rash	15%	21%
Skin disorder	8%	10%
Musculoskeletal and connective tissue disorders		
Hypertonia	33%	40%
Myalgia	14%	23%
Renal and urinary disorders		
Urinary urgency	8%	11%
Reproductive system and breast disorders		
Metrorrhagia*	7%	9%
Impotence**	6%	8%
General disorders and administration site conditions		
Injection site reaction (various kinds) [0]	26%	78%
Asthenia	48%	53%
Flu-like symptoms (complex)[§]	37%	57%
Pain	35%	42%

Chills	9%	21%
Peripheral edema	10%	12%
Chest pain	6%	9%
Malaise	3%	6%
Injection site necrosis	0%	4%

except for "injection site reaction (various kinds)[o]" and "flu-like symptom complex[§] " the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

[x] laboratory abnormality

* pre-menopausal women

** men

[o] "Injection site reaction (various kinds)" comprises all adverse events occurring at the injection site (except injection site necrosis), i.e., the following terms: injection site reaction, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site pain, injection site edema and injection site atrophy.

[§] "Flu-like symptom complex" denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating.

Laboratory Abnormalities

In the four clinical trials, leukopenia was reported in 18% and 6% of patients in Interferon beta-1b- and placebo-treated groups, respectively. No patients were withdrawn or dose reduced for neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Monitoring of complete blood and differential white blood cell counts is recommended [see Warnings and Precautions (5.6, 5.8)].

Other abnormalities included increase of SGPT to greater than five times baseline value (12%), and increase of SGOT to greater than five times baseline value (4%). In Study 1, two patients were dose reduced for increased hepatic enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of Interferon beta-1b patients were dose-reduced or interrupted treatment for increased hepatic enzymes. In Study 4, 1.7% of patients were withdrawn from treatment due to increased hepatic enzymes, two of them after a dose reduction. In Studies 1-4, nine (0.6%) patients were withdrawn from treatment with Interferon beta-1b for any laboratory abnormality, including four (0.3%) patients following dose reduction. Monitoring of liver function tests is recommended *[see Warnings and Precautions (5.7, 5.8)]*.

6.2 Postmarketing Experience

The following adverse events have been observed during postmarketing experience with Interferon beta-1b and are classified within body system categories:

Blood and lymphatic system disorders: Anemia, Thrombocytopenia

Endocrine disorders: Hypothyroidism, Hyperthyroidism, Thyroid dysfunction

Metabolism and nutrition disorders: Hypocalcemia, Hyperuricemia, Triglyceride increased, Anorexia, Weight decrease

Psychiatric disorders: Confusion, Depersonalization, Emotional lability

Nervous system disorders: Ataxia, Convulsion, Paresthesia, Psychotic symptoms

Cardiac disorders: Cardiomyopathy

Vascular disorders: Deep vein thrombosis, Pulmonary embolism

Respiratory, thoracic and mediastinal disorders: Bronchospasm, Pneumonia

Gastrointestinal disorders: Pancreatitis, Vomiting

Hepatobiliary disorders: Hepatitis, Gamma GT increased

Skin and subcutaneous tissue disorders: Pruritus, Skin discoloration, Urticaria

Renal and urinary disorders: Urinary tract infection, Urosepsis

General disorders and administration site conditions: Fatal capillary leak syndrome*.

*The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to Interferon beta-1b during Study 1 *[see Clinical Studies (14)]*. In patients receiving 0.25 mg every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. In Study 4 *[see Clinical Studies (14)]*, neutralizing activity was measured every 6 months and at end of study. At individual visits after start of therapy, activity was observed in 16.5% up to 25.2% of the Interferon beta-1b treated patients. Such neutralizing activity was measured at least once in 75 (29.9%) out of 251 Interferon beta-1b patients who provided samples during treatment phase; of these, 17 (22.7%) converted to negative status later in the study.

Based on all the available evidence, the relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Interferon beta-1b using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Interferon beta-

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