

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SYLATRON™ (peginterferon alfa-2b) for injection, for subcutaneous use Initial U.S. Approval: 2011

WARNING: DEPRESSION AND OTHER NEUROPSYCHIATRIC DISORDERS
See full prescribing information for complete boxed warning.
The risk of serious depression, with suicidal ideation and completed suicides, and other serious neuropsychiatric disorders are increased with alpha interferons, including SYLATRON. Permanently discontinue SYLATRON in patients with persistently severe or worsening signs or symptoms of depression, psychosis, or encephalopathy. These disorders may not resolve after stopping SYLATRON [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

RECENT MAJOR CHANGES

Warnings and Precautions
Depression and Other Serious Neuropsychiatric Adverse Reactions (5.1) 5/2015

INDICATIONS AND USAGE

SYLATRON is an alpha interferon indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. (1)

DOSAGE AND ADMINISTRATION

- 6 mcg/kg/week subcutaneously for 8 doses followed by;
- 3 mcg/kg/week subcutaneously for up to 5 years. (2.1)

DOSAGE FORMS AND STRENGTHS

- 200 mcg of deliverable lyophilized powder per single-use vial (3)
- 300 mcg of deliverable lyophilized powder per single-use vial (3)
- 600 mcg of deliverable lyophilized powder per single-use vial (3)

CONTRAINDICATIONS

- Known serious hypersensitivity reactions to peginterferon alfa-2b or interferon alfa-2b. (4)
- Autoimmune hepatitis. (4)
- Hepatic decompensation (Child-Pugh score >6 [class B and C]). (4)

WARNINGS AND PRECAUTIONS

- Depression and other serious neuropsychiatric adverse reactions. (5.1)
- History of significant or unstable cardiac disease. (5.2)
- Retinal disorders. (5.3)
- Child-Pugh score >6 (class B and C). (4, 5.4)
- Hypothyroidism, hyperthyroidism, hyperglycemia, diabetes mellitus that cannot be effectively treated by medication. (4, 5.5)

ADVERSE REACTIONS

Most common adverse reactions (>60%) are: fatigue, increased ALT, increased AST, pyrexia, headache, anorexia, myalgia, nausea, chills, and injection site reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation at 1-800-526-4099 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs metabolized by cytochrome P-450 (CYP) enzymes: Monitor for potential increased toxicities of drugs with a narrow therapeutic range metabolized by CYP1A2 or CYP2D6 when coadministered with SYLATRON. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatrics: Safety and efficacy in patients <18 years old have not been established. (8.4)
- Renal Impairment: Reduce the dose of SYLATRON by 25% in patients with moderate renal impairment and 50% in patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. (2.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DEPRESSION AND OTHER NEUROPSYCHIATRIC DISORDERS

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
 2.1 Recommended Dosing
 2.2 Dose Modification Guidelines
 2.3 Preparation and Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
 5.1 Depression and Other Serious Neuropsychiatric Adverse Reactions
 5.2 Cardiovascular Adverse Reactions
 5.3 Retinopathy and Other Serious Ocular Adverse Reactions
 5.4 Hepatic Failure
 5.5 Endocrinopathies
6 ADVERSE REACTIONS
 6.1 Clinical Trials Experience
 6.2 Immunogenicity
 6.3 Postmarketing Experience

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
 8.1 Pregnancy
 8.3 Nursing Mothers
 8.4 Pediatric Use
 8.5 Geriatric Use
 8.6 Hepatic Impairment
 8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
 12.1 Mechanism of Action
 12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DEPRESSION AND OTHER NEUROPSYCHIATRIC DISORDERS

The risk of serious depression, with suicidal ideation and completed suicides, and other serious neuropsychiatric disorders are increased with alpha interferons, including SYLATRON. Permanently discontinue SYLATRON in patients with persistently severe or worsening signs or symptoms of depression, psychosis, or encephalopathy. These disorders may not resolve after stopping SYLATRON [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

1 INDICATIONS AND USAGE

SYLATRON™ is an alpha interferon indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

- The recommended starting dose is 6 mcg/kg/week subcutaneously for 8 doses, followed by 3 mcg/kg/week subcutaneously for up to 5 years.
- Premedicate with acetaminophen 500 to 1000 mg orally 30 minutes prior to the first dose of SYLATRON and as needed for subsequent doses.
- The recommended starting doses of SYLATRON in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) are listed in Table 1 [see Use in Specific Populations (8.7)]. No dose adjustment is needed for patients with a creatinine clearance (CLcr) > 50 mL/min/1.73m².

Table 1: Recommended Starting Dose for Moderate and Severe Renal Impairment and End-Stage Renal Disease

Degree of Renal Impairment	Creatinine Clearance (mL/min/1.73m ²)	Initial doses for 8 weeks	Follow-up doses for 5 years
Moderate	30 – 50	4.5 mcg/kg/week	2.25 mcg/kg/week
Severe	<30	3 mcg/kg/week	1.5 mcg/kg/week
End-Stage Renal Disease	On dialysis	3 mcg/kg/week	1.5 mcg/kg/week

2.2 Dose Modification Guidelines

Guidelines for Dose Modification provided below are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 2.0).

- Permanently discontinue SYLATRON for:
 - Persistent or worsening severe neuropsychiatric disorders
 - Grade 4 non-hematologic toxicity
 - Inability to tolerate a dose of 1 mcg/kg/wk
 - New or worsening retinopathy
- Withhold SYLATRON dose for any of the following:
 - Absolute Neutrophil Count (ANC) less than $0.5 \times 10^9/L$
 - Platelet Count (PLT) less than $50 \times 10^9/L$
 - ECOG PS greater than or equal to 2
 - Non-hematologic toxicity greater than or equal to Grade 3
- Resume dosing at a reduced dose (see Table 1) when all of the following are present:
 - Absolute Neutrophil Count (ANC) greater than or equal to $0.5 \times 10^9/L$
 - Platelet Count (PLT) greater than or equal to $50 \times 10^9/L$
 - ECOG PS 0-1
 - Non-hematologic toxicity has completely resolved or improved to Grade 1

Table 2: SYLATRON Dose Modifications

Starting Dose	Dose Modifications for Doses 1 to 8
6 mcg/kg/week	First Dose Modification: 3 mcg/kg/week
	Second Dose Modification: 2 mcg/kg/week
	Third Dose Modification: 1 mcg/kg/week
	Permanently discontinue if unable to tolerate 1 mcg/kg/week
Starting Dose	Dose Modifications for Doses 9 to 260
3 mcg/kg/week	First Dose Modification: 2 mcg/kg/week
	Second Dose Modification: 1 mcg/kg/week
	Permanently discontinue if unable to tolerate 1 mcg/kg/week

2.3 Preparation and Administration

Reconstitute SYLATRON with 0.7 mL of Sterile Water for Injection, USP.

Table 3: Reconstitution of SYLATRON Single-Use Vials

SYLATRON Single-Use Vial		Diluent (Sterile Water for Injection, USP)		Deliverable Product and Volume	Final Concentration
200 mcg*	add	0.7 mL	=	200 mcg in 0.5 mL	40 mcg/0.1 mL
300 mcg [†]	add	0.7 mL	=	300 mcg in 0.5 mL	60 mcg/0.1 mL
600 mcg [‡]	add	0.7 mL	=	600 mcg in 0.5 mL	120 mcg/0.1 mL

*Total vial content of SYLATRON is 296 mcg.

[†]Total vial content of SYLATRON is 444 mcg.

[‡]Total vial content of SYLATRON is 888 mcg.

- Swirl gently to dissolve the lyophilized powder. **DO NOT SHAKE.**
- Visually inspect the solution for particulate matter and discoloration prior to administration. Discard if solution is discolored, cloudy, or if particulates are present.
- Do not withdraw more than 0.5 mL of reconstituted solution from each vial.
- Administer SYLATRON subcutaneously. Rotate injection sites.
- If reconstituted solution is not used immediately, store at 2°-8°C (36°-46°F) for no more than 24 hours. Discard reconstituted solution after 24 hours. **DO NOT FREEZE.**
- For single-use only. **DISCARD ANY UNUSED PORTION.**

3 DOSAGE FORMS AND STRENGTHS

- 200 mcg of deliverable lyophilized powder per single-use vial
- 300 mcg of deliverable lyophilized powder per single-use vial
- 600 mcg of deliverable lyophilized powder per single-use vial

4 CONTRAINDICATIONS

SYLATRON is contraindicated in patients with:

- A history of anaphylaxis to peginterferon alfa-2b or interferon alfa-2b
- autoimmune hepatitis
- hepatic decompensation (Child-Pugh score >6 [class B and C])

5 WARNINGS AND PRECAUTIONS**5.1 Depression and Other Serious Neuropsychiatric Adverse Reactions**

Peginterferon alfa-2b can cause life-threatening or fatal neuropsychiatric reactions. These include suicide, suicidal and homicidal ideation, depression, and an increased risk of relapse of recovering drug addicts. In the clinical trial, depression occurred in

59% of SYLATRON-treated patients and 24% of patients in the observation group. Depression was severe or life threatening in 7% of SYLATRON-treated patients compared with <1% of patients in the observation arm.

In post-marketing experience, neuropsychiatric adverse reactions have been reported up to 6 months after discontinuation of peginterferon alfa-2b. Based on post-marketing experience with peginterferon alfa-2b and interferon alfa-2b, treatment may also result in aggressive behavior, psychoses, hallucinations, bipolar disorders, mania, and encephalopathy.

Advise patients and their caregivers to immediately report any symptoms of depression or suicidal ideation to their healthcare provider. Monitor and evaluate patients for signs and symptoms of depression and other psychiatric symptoms every 3 weeks during the first 8 weeks of treatment and every 6 months thereafter. Monitor patients during treatment and for at least 6 months after the last dose of SYLATRON. Permanently discontinue SYLATRON for suicidal or homicidal ideation, aggressive behavior towards others, or other severe or persistent psychiatric symptoms; institute psychiatric intervention and follow-up as appropriate.

5.2 Cardiovascular Adverse Reactions

In the clinical trial, cardiac adverse reactions, including myocardial infarction, bundle-branch block, ventricular tachycardia, and supraventricular arrhythmia occurred in 4% of SYLATRON-treated patients compared with 2% of patients in the observation group. In post-marketing experience, hypotension, cardiomyopathy, and angina pectoris have occurred in patients treated with peginterferon alfa-2b.

Permanently discontinue SYLATRON for new onset of ventricular arrhythmia or cardiovascular decompensation.

5.3 Retinopathy and Other Serious Ocular Adverse Reactions

Peginterferon alfa-2b can cause decrease in visual acuity or blindness due to retinopathy. Retinal and ocular changes include macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment may be induced or aggravated by treatment with peginterferon alfa-2b or other alpha interferons. In the clinical study, two SYLATRON-treated patients developed partial loss of vision due to retinal thrombosis (n=1) or retinopathy (n=1). The overall incidence of serious retinal disorders, visual disturbances, blurred vision, and reduction in visual acuity was <1% in both SYLATRON-treated patients and the observation group.

Perform an eye examination that includes assessment of visual acuity and indirect ophthalmoscopy or fundus photography at baseline in patients with preexisting retinopathy and at any time during SYLATRON treatment in patients who experience changes in vision. Permanently discontinue SYLATRON in patients who develop new or worsening retinopathy.

5.4 Hepatic Failure

Peginterferon alfa-2b, increases the risk of hepatic decompensation and death in patients with cirrhosis. Monitor hepatic function with serum bilirubin, ALT, AST, alkaline phosphatase, and LDH at 2 and 8 weeks, and 2 and 3 months following initiation of SYLATRON, then every 6 months while receiving SYLATRON. Permanently discontinue SYLATRON for evidence of severe (Grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]) [see *Contraindications (4)*].

5.5 Endocrinopathies

Peginterferon alfa-2b can cause new onset or worsening of hypothyroidism, hyperthyroidism, and diabetes mellitus. In the clinical study, 1% of patients developed hypothyroidism; the overall incidence of endocrine disorders was 2% in SYLATRON-treated patients compared to <1% for patients in the observation group.

Obtain TSH levels within 4 weeks prior to initiation of SYLATRON, at 3 and 6 months following initiation, then every 6 months thereafter while receiving SYLATRON. Permanently discontinue SYLATRON in patients who develop hypothyroidism, hyperthyroidism or diabetes mellitus that cannot be effectively managed.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Depression and Other Neuropsychiatric Adverse Reactions [see *Warnings and Precautions (5.1)*]
- Cardiovascular Adverse Reactions [see *Warnings and Precautions (5.2)*]
- Retinopathy and Other Serious Ocular Adverse Reactions [see *Warnings and Precautions (5.3)*]
- Hepatic Failure [see *Warnings and Precautions (5.4)*]
- Endocrinopathies [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to SYLATRON in 608 patients with surgically resected, AJCC Stage III melanoma. SYLATRON was studied in an open label, multicenter, randomized, observation controlled trial. The median age of the population was 50 years with 10% of patients 65 years or older, and 42% were female. Fourteen percent of patients completed the 5 year treatment schedule.

Patients randomized to SYLATRON were to receive total doses of 48 mcg/kg (6 mcg/kg subcutaneous once weekly for 8 doses), and 780 mcg/kg (3 mcg/kg subcutaneous once weekly until disease recurrence or for up to 5 years), as tolerated. The median total dose received was 42 mcg/kg (range: 6 to 78 mcg/kg) for the first 8 doses, and 136 mcg/kg (range: 1 to 774 mcg/kg) for doses 9 to 260.

Serious adverse events were reported in 199 (33%) patients who received SYLATRON and 94 (15%) patients in the observation group.

The most common adverse reactions experienced by SYLATRON-treated patients were fatigue (94%), increased ALT (77%), increased AST (77%), pyrexia (75%), headache (70%), anorexia (69%), myalgia (68%), nausea (64%), chills (63%), and injection site reaction (62%). The most common serious adverse reactions were fatigue (7%), increased ALT (3%), increased AST (3%), and pyrexia (3%) in the SYLATRON-treated group vs. <1% in the observation group for these reactions.

Thirty three percent of patients receiving SYLATRON discontinued treatment due to adverse reactions. The most common adverse reactions present at the time of treatment discontinuation were fatigue (27%), depression (17%), anorexia (15%), increased ALT (14%), increased AST (14%), myalgia (13%), nausea (13%), headache (13%), and pyrexia (11%). Adverse events that occurred in the clinical study at $\geq 5\%$ incidence in the SYLATRON-treated group and with a greater incidence in patients receiving SYLATRON as compared to the observation group are presented in **Table 4**.

Table 4: Incidence of Adverse Reactions^(*) Occurring in $\geq 5\%$ of Melanoma Patients Treated with SYLATRON and with a Greater Incidence as Compared to Observation

Adverse Reaction	SYLATRON N=608		Observation N=628	
	All Grades (%)	Grade 3 and 4 (%)	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reaction	100	51	82	18
General Disorders and Administrative Site Conditions				
Fatigue	94	16	41	1
Pyrexia	75	4	9	0
Chills	63	1	6	0
Injection Site Reaction	62	1.8	0	0
Metabolic/Laboratory				
ALT or AST Increased	77	11	26	1
Blood Alkaline Phosphatase Increased	23	0	11	<1
Weight Decreased	11	<1	1	<1
GGT Increased	8	4	1	<1
Proteinuria	7	0	3	0
Anemia	6	<1	2	<1
Nervous System Disorders				
Headache	70	4	19	1
Dysgeusia	38	0	1	0
Dizziness	35	2	11	<1
Olfactory Nerve Disorder	23	0	1	0
Paraesthesia	21	<1	14	<1
Metabolism and Nutrition Disorders				
Anorexia	69	3	13	0
Musculoskeletal and Connective Tissue Disorders				
Myalgia	68	4	23	<1
Arthralgia	51	3	22	1
Gastrointestinal Disorders				
Nausea	64	3	11	<1
Diarrhea	37	1	8	<1
Vomiting	26	1	4	0
Psychiatric Disorders				

Adverse Reaction	SYLATRON N=608		Observation N=628	
	Depression	59	7	24
Skin and Subcutaneous Tissue Disorders				
Exfoliative Rash	36	1	4	0
Alopecia	34	0	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	6	1	2	1
Cough	5	<1	2	0

* Adverse reactions were graded using NCI CTCAE, V.2.0.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In a clinical study conducted in patients with melanoma, the incidence of binding antibodies to peg-interferon alfa-2b was approximately 35% (50/144 patients). Among the patients who tested positive for binding antibodies, one patient developed neutralizing antibodies. The impact of antibody formation on pharmacokinetics, safety and efficacy of peg-interferon alfa-2b could not be assessed based on limited available data.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SYLATRON with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of peginterferon alfa-2b as monotherapy and in combination with ribavirin in chronic hepatitis C (CHC) patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders

pure red cell aplasia, thrombotic thrombocytopenic purpura

Ear and Labyrinth Disorders

hearing loss, vertigo, hearing impairment

Endocrine Disorders

diabetic ketoacidosis

Eye Disorders

Vogt-Koyanagi-Harada syndrome

Gastrointestinal Disorders

aphthous stomatitis, pancreatitis, colitis

Infusion reactions

angioedema, urticaria, bronchoconstriction

Immune System Disorders

systemic lupus erythematosus, erythema multiforme, thyroiditis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid arthritis, interstitial nephritis, and systemic lupus erythematosus

Infections

sepsis

Metabolism and Nutrition Disorders

hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, myositis

Nervous System Disorders

seizures, memory loss, peripheral neuropathy, paraesthesia, migraine headache

Respiratory, Thoracic and Mediastinal Disorders

dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, sarcoidosis, pulmonary hypertension, and pulmonary fibrosis

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis

Vascular Disorders

hypertension, hypotension, stroke

7 DRUG INTERACTIONS

Peginterferon alfa-2b inhibits CYP1A2 and CYP2D6 activity. When caffeine (CYP1A2 substrate) or desipramine (CYP2D6 substrate) was coadministered with peginterferon alfa-2b (3 mcg/kg once weekly for two weeks), the exposure to caffeine increased 36% and the exposure to desipramine increased 30% as compared to when caffeine or desipramine was administered alone. Monitor for potential increased toxicities of drugs with a narrow therapeutic range metabolized by CYP1A2 or CYP2D6 when coadministered with SYLATRON. [See *Clinical Pharmacology* (12.3).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of SYLATRON in pregnant women. Nonpegylated interferon alfa-2b was an abortifacient in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million international units (IU)/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60-kg adult). The estimated Intron A human equivalent dose of 5 to 10 million IU/kg daily is approximately equal to a human equivalent dose of 79 to 158 mcg/kg/week of SYLATRON. Use SYLATRON during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether the components of SYLATRON are excreted in human milk. Studies in mice have shown that mouse interferons are excreted in breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the SYLATRON treatment, taking into account the importance of the therapy to the mother.

8.4 Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Clinical studies of SYLATRON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

SYLATRON has not been studied in patients with melanoma who have hepatic impairment. In patients treated for viral hepatitis, peginterferon alfa-2b treatment is contraindicated in those with moderate or severe hepatic impairment (Child-Pugh scores >6). Discontinue SYLATRON if hepatic decompensation (Child-Pugh scores >6) occurs during treatment. [See *Contraindications* (4) and *Warnings and Precautions* (5.4).]

8.7 Renal Impairment

Reduce the dose of SYLATRON by 25% in patients with moderate renal impairment (CL_{cr} 30 to 50 mL/min/1.73m²) and 50% in patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73m²) or ESRD requiring dialysis [see *Dosage and Administration* (2.1)]. A study in subjects with varying degrees of renal impairment showed that the mean exposure (AUC) to peginterferon alfa-2b increased in subjects with moderate and severe renal impairment or ESRD requiring dialysis, as compared to subjects with normal renal function (CL_{cr} > 80 mL/min/1.73m²) following a single 4.5 mcg/kg dose of peginterferon alfa-2b [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

The experience with overdose of SYLATRON is limited. Patients who were over dosed experienced the following adverse reactions: severe fatigue, headache, myalgia, neutropenia, and thrombocytopenia. The highest single dose administered was 14 mcg/kg.

11 DESCRIPTION

SYLATRON, peginterferon alfa-2b, is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The average molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the SYLATRON molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alfa-2b is approximately 0.7 x 10⁸ international units/mg protein.

Interferon alfa-2b is a protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

Each vial contains either 296 mcg, 444 mcg or 888 mcg of peginterferon alfa-2b as a sterile, white to off-white lyophilized powder, and dibasic sodium phosphate anhydrous (1.11 mg), monobasic sodium phosphate dihydrate (1.11 mg), polysorbate 80 (0.074 mg), and sucrose (59.2 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Peginterferon alfa-2b is a pleiotropic cytokine; the mechanism by which it exerts its effects in patients with melanoma is unknown.

12.3 Pharmacokinetics

The pharmacokinetics was studied in 32 patients receiving adjuvant therapy for melanoma with SYLATRON according to the recommended dose and schedule (6 mcg/kg/week for 8 doses, followed by 3 mcg/kg/week thereafter). At a dose of 6 mcg/kg/week once weekly, the geometric mean C_{max} was 4.4 ng/mL (CV 51%) and the geometric mean AUC_{tau} was 430 ng•hr/mL (CV 35%) at week 8. The mean terminal half-life was approximately 51 hours (CV 18%). The mean accumulation from week 1 to week 8 was 1.7. After administration of 3 mcg/kg/week once weekly, the mean geometric C_{max} was 2.5 ng/mL (CV 33%) and the geometric mean AUC_{tau} was 228 ng•hr/mL (CV 24%) at week 4. The mean terminal half-life was approximately 43 hours (CV 19%).

Renal Impairment:

Renal clearance accounts for approximately 30% of total peginterferon alfa-2b clearance. The effect of renal impairment on the pharmacokinetics of peginterferon alfa-2b was studied in 24 subjects with normal or impaired renal function after a single 4.5 mcg/kg dose. Compared to subjects with normal renal function ($CL_{cr} > 80$ mL/min/1.73 m²), the geometric mean AUC_{last} to peginterferon alfa-2b increased by 1.4-fold in subjects with moderate renal impairment (CL_{cr} 30 to 50 mL/min/1.73m²) and 2.1-fold in subjects with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73m²) or ESRD requiring dialysis [see *Use in Specific Populations* (8.7)].

No clinically meaningful amounts of peginterferon alfa-2b were removed during hemodialysis following a single 1 mcg/kg dose in subjects with renal impairment.

Drug Interactions:

Peginterferon alfa-2b inhibits CYP1A2 and CYP2D6 activity. In a drug interaction study, healthy subjects received a dose of 200 mg of caffeine (CYP1A2 substrate), 2 mg of midazolam (CYP3A4 substrate), 500 mg of tolbutamide (CYP2C9 substrate), or 50 mg of desipramine (CYP2D6 substrate) before and after two doses of SYLATRON administered subcutaneously at a dose of 3 mcg/kg. The geometric mean AUC_{last} was increased by 36% for caffeine and 30% for desipramine when coadministered with SYLATRON compared to caffeine or desipramine administered alone. No clinically meaningful changes in CYP2C9 activity and CYP3A4 activity were observed. [See *Drug Interactions* (7).]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis:

SYLATRON has not been tested for its carcinogenic potential. Neither peginterferon alfa-2b nor its components, interferon or methoxypolyethylene glycol, caused damage to DNA when tested in the standard battery of mutagenesis assays, in the presence and absence of metabolic activation.

Impairment of Fertility:

SYLATRON may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m² peginterferon alfa-2b alone every other day for 1 month (approximately 72 to 144 times the recommended weekly human dose based upon body surface area). These effects included transiently decreased serum levels of estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and serum hormone levels resumed in these animals 2 to 3 months following cessation of peginterferon alfa-2b treatment. Every other day dosing with 262 mcg/m² (approximately 3.5 to 7 times the recommended weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of SYLATRON on male fertility have not been studied.

14 CLINICAL STUDIES

The safety and effectiveness of SYLATRON were evaluated in an open-label, multicenter, randomized (1:1) study conducted in 1256 patients with surgically resected, AJCC Stage III melanoma within 84 days of regional lymph node dissection. Patients were randomized to observation (no therapy) (n=629) or to SYLATRON (n=627) at a dose of 6 mcg/kg by subcutaneous injection once weekly for 8 doses followed by a 3 mcg/kg subcutaneous injection once weekly for a period of up to 5 years total treatment. The dose of SYLATRON was adjusted to maintain an ECOG Performance Status of 0 to 1.

The median age of the population was 50 years with 11% of patients 65 years or older, and 42% were female. Forty percent of the study population had microscopic, nonpalpable nodal involvement and 59% had clinically palpable nodes prior to lymphadenectomy. A total of 54% of subjects had one pathologically positive lymph node, 34% had 2 to 4 positive nodes, and 12% had 5 or more. Most subjects had no second primary lesion (98%). Ulceration of the primary lesion was present in 30% of subjects (52% had no ulceration of the primary lesion, and the status was missing/unknown for 18% of subjects). The most common sites were the trunk (43%) or the leg (32%). Eighty-four percent had an International Prognostic Index (IPI) score of 0 and 16% had an IPI score of 1. The main outcome measure was relapse-free survival (RFS), defined as the time from randomization to the earliest date of any relapse (local, regional, in-transit, or distant), or death from any cause. Secondary outcome measures included overall survival.

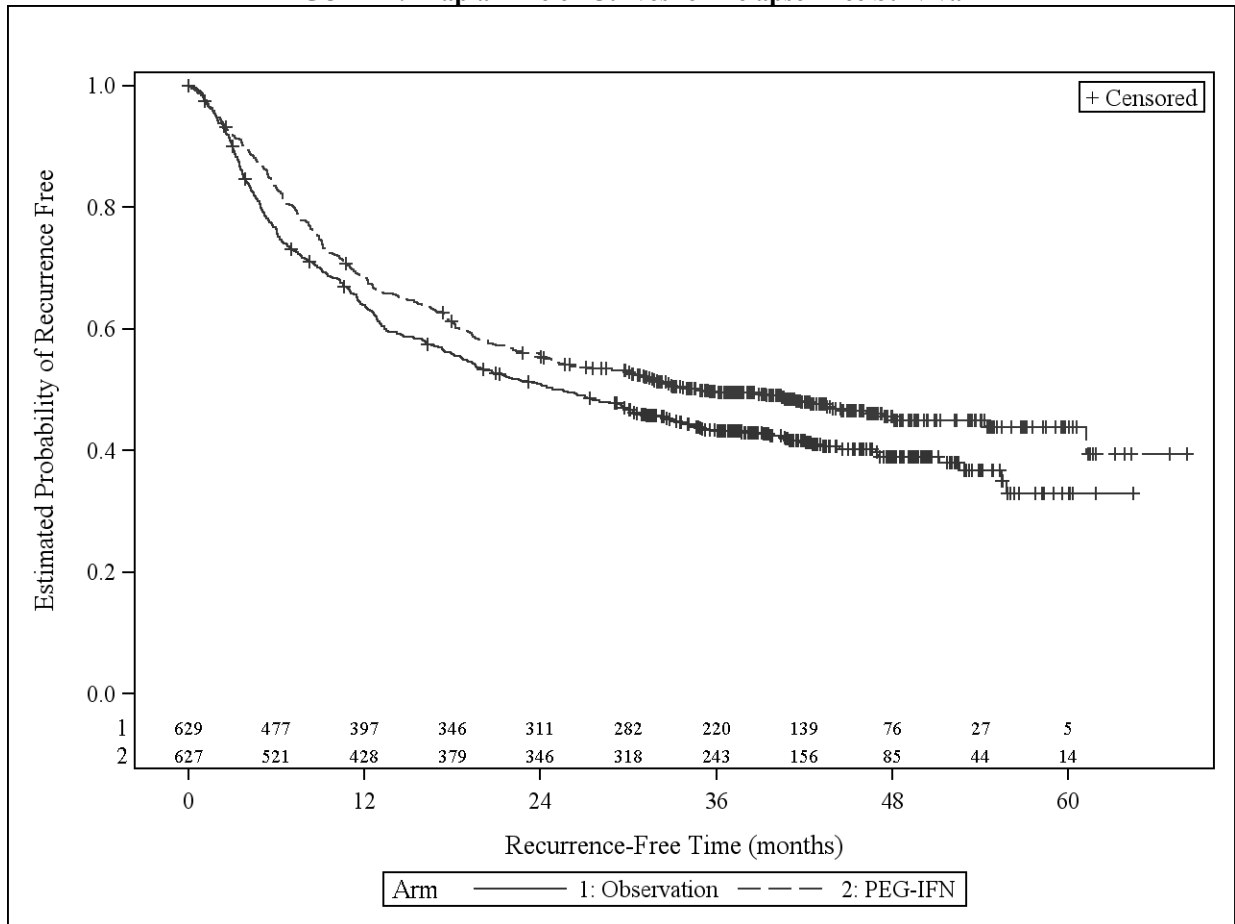
Patients in the SYLATRON arm received 6 mcg/kg/week for a median of 8.0 weeks. Less than 1% of patients took longer than 9 weeks to complete the 6 mcg/kg/week dosing regimen. Approximately one-third (36%) of patients required dose reductions and 29%

of patients required a dose delay, with an average delay of 1.2 weeks, during the initial 8 weeks of SYLATRON. Ninety-four patients (16%) did not continue on to the 3 mcg/kg/week dosing regimen.

Patients who continued on SYLATRON after the initial 8 doses, received 3 mcg/kg/week for a median duration of treatment of 14.3 months. Approximately half (52%) of the patients underwent dose reductions and 70% required dose delays (average delay 2.2 weeks).

Based on 696 RFS events, determined by the Independent Review Committee, median RFS was 34.8 months (95% CI: 26.1, 47.4) and 25.5 months (95% CI: 19.6, 30.8) in the SYLATRON and observation arms, respectively. The estimated hazard ratio for RFS was 0.82 (95% CI: 0.71, 0.96; unstratified log-rank $p=0.011$) in favor of SYLATRON. Figure 1 shows the Kaplan-Meier curves of RFS.

FIGURE 1: Kaplan-Meier Curves for Relapse-Free Survival



There was no statistically significant difference in survival between the SYLATRON and the observation arms. Based on 525 deaths, the estimated hazard ratio of SYLATRON versus observation was 0.98 (95% CI: 0.82, 1.16).

16 HOW SUPPLIED/STORAGE AND HANDLING

Each SYLATRON Package Contains:	
A box containing one 200 mcg per vial of SYLATRON powder and one 1.25 mL vial of Sterile Water for Injection, USP, 2 B-D Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1388-01)
A box containing one 300 mcg per vial of SYLATRON powder and one 1.25 mL vial of Sterile Water for Injection, USP, 2 B-D Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1287-02)
A box containing one 600 mcg per vial of SYLATRON powder and one 1.25 mL vial of Sterile Water for Injection, USP, 2 B-D Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1312-01)
Each SYLATRON PACK 4 Contains:	
A box containing four 200 mcg per vial of SYLATRON powder and four 1.25 mL vials of Sterile Water for Injection, USP, 8 B-D Safety Lok syringes with a safety sleeve and 8 alcohol swabs.	(NDC 0085-1388-02)
A box containing four 300 mcg per vial of SYLATRON powder and four 1.25 mL vials of Sterile Water for Injection, USP, 8 B-D Safety Lok syringes with a safety sleeve and 8 alcohol swabs.	(NDC 0085-1287-03)

Storage:

SYLATRON should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]. **DO NOT FREEZE.**

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Instructions for Use and Medication Guide).

- Advise patients that SYLATRON may be administered with antipyretics at bedtime to minimize common “flu-like” symptoms (including chills, fever, muscle aches, joint pain, headaches, tiredness).
- Advise patients to maintain hydration if experiencing “flu-like” symptoms.
- Advise patients and their caregivers to immediately report any symptoms of depression or suicidal ideation to their healthcare provider during treatment and up to 6 months after the last dose.
- Use SYLATRON during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.1)*].
- Instruct patients to not re-use or share syringes and needles.
- Instruct patients on proper disposal of vials, syringes and needles.

Manufactured by: Schering Corporation, a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

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For patent information: www.merck.com/product/patent/home.html

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