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)]*.

---------- 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----------

- 296 mcg lyophilized powder per single-use vial
- 444 mcg lyophilized powder per single-use vial
- 888 mcg lyophilized powder per single-use vial

---------- 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----------

- Drug metabolized by cytochrome P-450 (CYP) enzymes: Monitor closely when used in combination with drugs metabolized by CYP2C9 or CYP2D6. (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: Increase frequency of monitoring for SYLATRON toxicity in patients with moderate and severe renal impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 Dose

- 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.

2.2 Dose Modification

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) $<0.5x10^9$/L
  - Platelet Count (PLT) $<50x10^9$/L
  - ECOG PS ≥2
  - Non-hematologic toxicity ≥ Grade 3

- Resume dosing at a reduced dose (see Table 1) when all of the following are present:
  - Absolute Neutrophil Count (ANC) $\geq 0.5x10^9$/L
  - Platelet Count (PLT) $\geq 50x10^9$/L
  - ECOG PS 0-1
  - Non-hematologic toxicity has completely resolved or improved to Grade 1

TABLE 1: 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.

Upon reconstitution, the final concentration of SYLATRON will be

- 40 mcg per each 0.1 mL for vials containing 296 mcg of SYLATRON
- 60 mcg per each 0.1 mL for vials containing 444 mcg of SYLATRON
- 120 mcg per each 0.1 mL for vials containing 888 mcg of SYLATRON

- 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

- 296 mcg lyophilized powder per single-use vial
- 444 mcg lyophilized powder per single-use vial
- 888 mcg 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 persistent severe or worsening psychiatric symptoms or behaviors and refer for psychiatric evaluation.

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

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.

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.

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 ≥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 2**.

TABLE 2: Incidence of Adverse Reactions(†) Occurring in ≥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				
Depression	59	7	24	<1
Skin and Subcutaneous Tissue Disorders				
Exfoliative Rash	36	1	4	0
Alopecia	34	0	1	0
Respiratory, Thoracic and				

Adverse Reaction	SYLATRON N=608		Observation N=628	
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 and pulmonary hypertension

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis

Vascular Disorders

hypertension, hypotension, stroke

7 DRUG INTERACTIONS

In healthy subjects who were administered peginterferon alfa-2b subcutaneously at 1 mcg/kg once weekly for four weeks with probe drugs of metabolic enzymes administered before the first dose and after the fourth dose, a measure of CYP2C9 activity increased to 125% of baseline, whereas a measure of CYP2D6 activity decreased to 51% of baseline *[see Clinical Pharmacology (12.3)]*.

When administering SYLATRON with medications metabolized by CYP2C9 or CYP2D6, the therapeutic effect of these drugs may be altered.

The effects of pegylated interferon alfa-2b on the pharmacokinetics of drugs metabolized by cytochrome P-450 enzymes have not been studied at the higher clinical doses for patients with melanoma (3 mcg/kg/week and 6 mcg/kg/week).

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

The mean area under the concentration-time curve (AUC_{last}) following a single dose of peginterferon alfa-2b at 1 mcg/kg increased by 1.3-, 1.7- and 1.9-fold in subjects with mild (creatinine clearance 50-79 mL/min), moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance 10-29 mL/min) renal impairment, respectively. After multiple doses, the mean AUC_{tau} increased by 1.3-fold in moderate and 2.1-fold in severe renal impairment. No clinical meaningful amounts of peginterferon alfa-2b were removed during hemodialysis. Dose reductions of 25% and 50% are recommended in patients with moderate and severe renal impairment, respectively, receiving alpha interferons for chronic hepatitis C.

The effect of varying degrees of renal impairment on the pharmacokinetics of peginterferon alfa-2b at the recommended doses of 3 mcg/kg or 6 mcg/kg for patients with melanoma has not been studied.

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 10^8 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). Following reconstitution with 0.7 mL of Sterile Water for Injection USP, each vial contains SYLATRON at 40 mcg per 0.1 mL, 60 mcg per 0.1 mL, or 120 mcg per 0.1 mL.

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 were 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 Dysfunction:

The disposition of peginterferon alfa-2b was studied in 26 subjects with varying degrees of renal function after administration of a single subcutaneous dose of peginterferon alfa-2b at 1 mcg/kg. Renal clearance accounts for approximately 30% of total peginterferon alfa-2b clearance. The AUC_{last} increased by 1.3-, 1.7- and 1.9-fold in mild, moderate and severe renal impairment, respectively. The mean elimination half-life and maximal plasma concentration (C_{max}) increased in subjects with renal impairment. The mean AUC_{last} was similar in subjects with severe renal impairment on and not on hemodialysis, suggesting that no clinical meaningful amounts of peginterferon alfa-2b were removed during hemodialysis.

After subcutaneous administration of 1 mcg/kg of peginterferon alfa-2b once weekly for four weeks in 21 subjects with varying degrees of renal function, AUC_{tau} at week 4 increased 1.3-fold in moderate and 2.1-fold in severe renal impairment. The C_{max} at week 4 increased 1.8-fold in severe renal impairment, but no difference was observed in moderate renal impairment *[see Use in Specific Populations (8.7)]*.

The effect of varying degrees of renal impairment on pharmacokinetics of peginterferon alfa-2b at 3 mcg/kg and 6 mcg/kg recommended for patients with melanoma has not been studied.

Drug Interactions:

In a two-way crossover trial, 12 healthy subjects were administered probe drugs of metabolic enzymes: caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), midazolam (CYP3A4), and dapsone (N-acetyltransferase, NAT), with or without a single subcutaneous (SC) dose of peginterferon alfa-2b at 1 mcg/kg. The results suggest that single doses of peginterferon alfa-2b do not affect activities of CYP1A2, CYP2C9, CYP2D6, CYP3A4 and NAT enzymes.

In 24 healthy subjects, the effect of subcutaneous doses of peginterferon alfa-2b at 1 mcg/kg/week for 4 weeks on the pharmacokinetics of caffeine, tolbutamide, dextromethorphan and midazolam were studied. A measure of CYP2C9 activity increased to 125% (90% CI: 116% to 135%) of baseline, whereas a measure of CYP2D6 activity decreased to 51% (90% CI: 38% to 67%) of baseline when coadministered with peginterferon alfa-2b at week 4, indicating that peginterferon alfa-2b may affect the metabolism of CYP2C9 and CYP2D6 drugs. A measure of CYP1A2 and CYP3A4 activity did not show clinically meaningful changes.

When patients are administered SYLATRON with medications metabolized by CYP2C9 or CYP2D6, the therapeutic effect of these drugs may be altered.

The effects of peginterferon alfa-2b at the clinical doses for melanoma (3 mcg/kg/week and 6 mcg/kg/week) on the systemic exposure of drugs metabolized by cytochrome P-450 enzymes have not been studied *[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/m^2 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/m^2 (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.

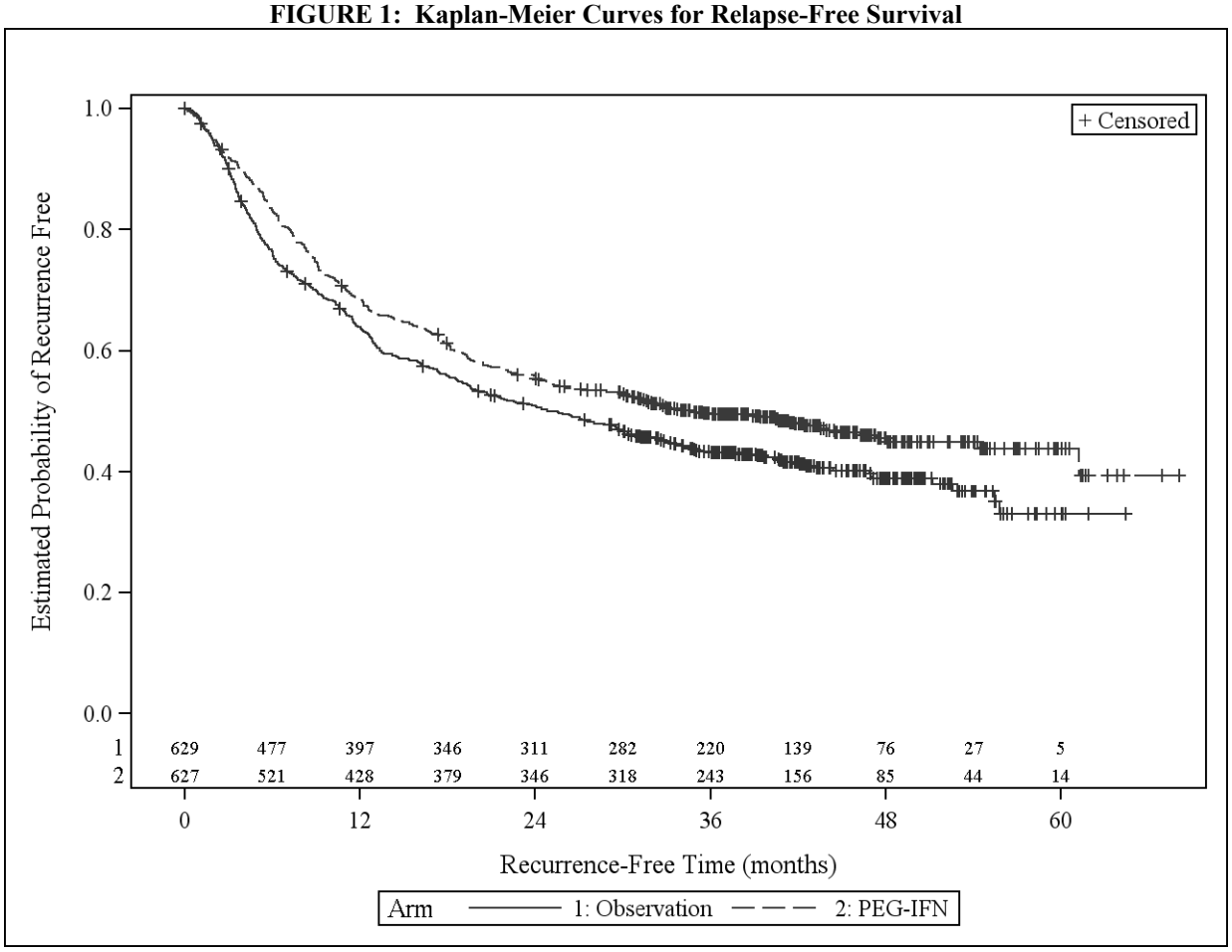
The median age of the population was 50 years with 11% of patients 65 years or older, and 42% were female. Forty percent of the study population had microscopic, nonpalpable nodal involvement and 59% had clinically palpable nodes prior to lymphadenectomy. A total of 54% of subjects had one pathologically 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 296 mcg 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 444 mcg 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 888 mcg 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 296 mcg vials 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 444 mcg vials 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)
A box containing four 888 mcg vials 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 0085-1312-02)

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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