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PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT featuring SYLATRON™ (peginterferon alfa-2b) for injection, for subcutaneous use. Merck, the maker of SYLATRON, has paid for these program materials to be developed and provided to you.

SYLATRON is indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.[1] SYLATRON demonstrated a significant, sustained improvement in relapse-free survival (RFS) in a pivotal clinical trial.[1] 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 group treated with SYLATRON and the observation group, 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. There was no statistically significant difference in survival between the group receiving SYLATRON and the observation arm. Based on 525 deaths, the estimated hazard ratio of SYLATRON versus observation was 0.98 (95% CI: 0.82, 1.16) (please see study design in linked document [Prescribing Information] below).[1]

SELECT IMPORTANT SAFETY 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.

SYLATRON is contraindicated in patients with a history of anaphylaxis to peginterferon alfa-2b or interferon alfa-2b, in patients with autoimmune hepatitis, and in patients with hepatic decompensation (Child-Pugh score >6 [class B and C]).

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

Cardiac adverse reactions, including myocardial infarction, bundle-branch block, ventricular tachycardia, and supraventricular arrhythmia occurred in 4% of patients treated with SYLATRON compared with 2% of patients in the observation group. 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.

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

(Select Important Safety Information continued on next page)

aggravated by treatment with peginterferon alfa-2b or other alpha interferons. The overall incidence of serious retinal disorders, visual disturbances, blurred vision, and reduction in visual acuity was <1% in both patients treated with SYLATRON™ (peginterferon alfa-2b) and those in 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.

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 at 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]).

Peginterferon alfa-2b can cause new onset or worsening of hypothyroidism, hyperthyroidism, and diabetes mellitus. Hypothyroidism developed in 1% of patients treated with SYLATRON. The overall incidence of endocrine disorders was 2% in patients treated with SYLATRON 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.

The most common adverse reactions in patients treated with SYLATRON versus observation were fatigue (94% vs. 41%), increased ALT (77% vs. 26%), increased AST (77% vs. 26%), pyrexia (75% vs. 9%), headache (70% vs. 19%), anorexia (69% vs. 13%), myalgia (68% vs. 23%), nausea (64% vs. 11%), chills (63% vs. 6%), and injection site reaction (62% vs. 0%).

The most common serious adverse reactions in patients treated with SYLATRON versus observation were fatigue (7% vs. <1%), increased ALT (3% vs. <1%), increased AST (3% vs. <1%), and pyrexia (3% vs. <1%).

Thirty-three percent of patients receiving SYLATRON discontinued treatment due to adverse reactions.

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

There are no adequate and well-controlled studies of SYLATRON in pregnant women. Use SYLATRON during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether the components of SYLATRON are excreted in human 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 treatment with SYLATRON.

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

Increase frequency of monitoring for SYLATRON toxicity in patients with moderate and severe renal impairment.

Before prescribing SYLATRON, please read the Prescribing Information, including the Boxed Warning about depression and other neuropsychiatric disorders.

For additional copies of the Prescribing Information, please call 800-672-6372, visit sylatron.com, or contact your Merck representative.

More information regarding the use of SYLATRON is available in the current edition of *MPR*.

Sincerely,

Grace L. McBride
Editorial Director
MPR Custom Programs

REFERENCE

1. SYLATRON™ [Prescribing Information]. Kenilworth, NJ: Schering Corporation, a subsidiary of **Merck & Co., Inc.**; 2011.

SYLATRON™

(peginterferon alfa-2b) for injection, for subcutaneous use

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HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: DEPRESSION AND OTHER NEUROPSYCHIATRIC DISORDERS

See 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.

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.

DOSAGE AND ADMINSTRATION

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

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
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score >6 [class B and C])

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm.
- Pediatrics: Safety and efficacy in patients <18 years old have not been established.
- Renal Impairment: Increase frequency of monitoring for SYLATRON toxicity in patients with moderate and severe renal impairment.

For melanoma patients with microscopic or gross nodal involvement

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

Before prescribing SYLATRON, please read the Prescribing Information, including the Boxed Warning about depression and other neuropsychiatric disorders.

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Preparation of SYLATRON™ (peginterferon alfa-2b)

- Reconstitute SYLATRON with the provided 0.7 mL Sterile Water for Injection USP (**Table 1**).
- 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.
- 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 PORTIONS.

Table 1

PREPARATION AND ADMINISTRATION				
VIAL SIZE	**SYLATRON: PACKAGE NDC**	**SYLATRON: PACK 4 NDC**	**FINAL CONCENTRATION**	**MAXIMUM DOSE PER VIAL[a]**
			Upon reconstitution with 0.7 mL of supplied diluent	**0.5 mL**
296 mcg	0085-1388-01	0085-1388-02	40 mcg/0.1 mL	200 mcg
444 mcg	0085-1287-02	0085-1287-03	60 mcg/0.1 mL	300 mcg
888 mcg	0085-1312-01	0085-1312-02	120 mcg/0.1 mL	600 mcg

[a]Do not withdraw more than 0.5 mL of reconstituted solution from each vial.

An adjuvant treatment regimen designed for dosing flexibility

- Once-weekly subcutaneous dosing. Rotate injection sites.
- SYLATRON is administered at a weekly dose of 6 mcg/kg for Doses 1 to 8 then decreased to 3 mcg/kg weekly for up to 5 years.
- Premedicate with acetaminophen 500 mg to 1000 mg orally 30 minutes prior to the first dose and as needed for subsequent doses.
- Therapy may be administered in the health care provider's office or at home.

SELECT IMPORTANT SAFETY INFORMATION

- 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. Depression occurred in 59% of patients treated with SYLATRON and 24% of patients in the observation group. Depression was severe or life-threatening in 7% of patients treated with SYLATRON compared with <1% of patients in the observation arm. 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.
- Cardiac adverse reactions, including myocardial infarction, bundle-branch block, ventricular tachycardia, and supraventricular arrhythmia occurred in 4% of patients treated with SYLATRON compared with 2% of patients in the observation group. 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.
- 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. The overall incidence of serious retinal disorders, visual disturbances, blurred vision, and reduction in visual acuity was <1% in both patients treated with SYLATRON and those in 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.

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Dose modification guidelines for SYLATRON™ (peginterferon alfa-2b)

- Dose reduction protocol helps manage both hematologic and nonhematologic toxicities (**Figure 1**).
- Dose of SYLATRON may be gradually modified on a weekly basis (**Figure 2**).
- Dose of SYLATRON is adjusted to maintain an Eastern Cooperative Oncology Group Performance Status of 0 or 1.
- Dose of SYLATRON may need to be discontinued based on criteria in **Figure 1**; monitor patients during treatment and for at least 6 months after last dose of SYLATRON.

Figure 1

GUIDELINES FOR DOSE MODIFICATIONS	
INDICATOR	**INTERVENTION**
Hematologic toxicities	Withhold SYLATRON, then resume dosing at a reduced dose when all of the following are present: • Absolute neutrophil count ≥0.5x10^9/L • Platelet count ≥50x10^9/L • ECOG PS 0 or 1 • Nonhematologic toxicity has completely resolved or improved to Grade 1
Absolute neutrophil count <0.5x10^9/L Platelet count <50x10^9/L	
Nonhematologic toxicity	
≥Grade 3	
Performance status	
ECOG[a] performance status ≥2	
Permanently discontinue SYLATRON for: • Persistent or worsening severe neuropsychiatric disorders • Grade 4 nonhematologic toxicity • Inability to tolerate a dose of 1 mcg/kg/wk • New or worsening retinopathy	
[a]Eastern Cooperative Oncology Group	

Figure 2

DOSE MODIFICATIONS	
STARTING DOSE	**DOSE MODIFICATIONS FOR DOSES 1 TO 8**
6 mcg/kg/wk	First dose modification: 3 mcg/kg/wk
	Second dose modification: 2 mcg/kg/wk
	Third dose modification: 1 mcg/kg/wk
	Permanently discontinue if unable to tolerate 1 mcg/kg/wk
STARTING DOSE	**DOSE MODIFICATIONS FOR DOSES 9 TO 260**
3 mcg/kg/wk	First dose modification: 2 mcg/kg/wk
	Second dose modification: 1 mcg/kg/wk
	Permanently discontinue if unable to tolerate 1 mcg/kg/wk

SELECT IMPORTANT SAFETY INFORMATION (*continued*)

- 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 at 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]).
- Peginterferon alfa-2b can cause new onset or worsening of hypothyroidism, hyperthyroidism, and diabetes mellitus. Hypothyroidism developed in 1% of patients treated with SYLATRON. The overall incidence of endocrine disorders was 2% in patients treated with SYLATRON 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.

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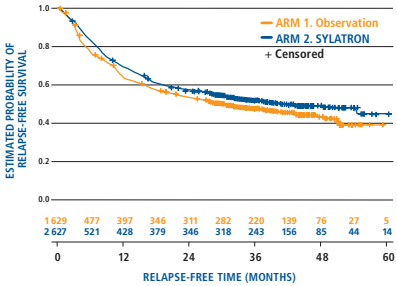
☑ Significant, sustained improvement in relapse-free survival (Figure 3)

Figure 3

KAPLAN-MEIER CURVES FOR RELAPSE-FREE SURVIVAL

Relapse-Free Survival (RFS) in Node-Positive Malignant Melanoma Patients—ITT Population



- SYLATRON™ (peginterferon alfa-2b) sustained RFS over observation throughout the study period.
  - Median RFS of 34.8 months (95% CI, 26.1–47.4) for SYLATRON vs 25.5 months (95% CI, 19.6–30.8) for observation
  - 18% reduction in the risk of relapse (HR = 0.82 [95% CI, 0.71–0.96], *P* = 0.011)
- There was no statistically significant difference in survival between groups. Based on 525 deaths, the estimated hazard ratio of SYLATRON vs observation was 0.98 (95% CI, 0.82–1.16).

Study Design: An open-label, multicenter study of 1,256 patients with stage III melanoma (intent-to-treat population). Patients were randomized within 84 days of regional lymph node dissection to either observation or SYLATRON at a dose of 6 mcg/kg subcutaneously once weekly for 8 doses, followed by 3 mcg/kg subcutaneously once weekly for a period of up to 5 years. The dose of SYLATRON was adjusted to maintain an ECOG Performance Status of 0 or 1. The main outcome measure was relapse-free survival, defined as the time from randomization to the earliest date of any relapse (local, regional, in-transit, or distant), or death from any cause.

SELECT IMPORTANT SAFETY INFORMATION (*continued*)

- The most common adverse reactions in patients treated with SYLATRON versus observation were fatigue (94% vs. 41%), increased ALT (77% vs. 26%), increased AST (77% vs. 26%), pyrexia (75% vs. 9%), headache (70% vs. 19%), anorexia (69% vs. 13%), myalgia (68% vs. 23%), nausea (64% vs. 11%), chills (63% vs. 6%), and injection site reaction (62% vs. 0%).
- The most common serious adverse reactions in patients treated with SYLATRON versus observation were fatigue (7% vs. <1%), increased ALT (3% vs. <1%), increased AST (3% vs. <1%), and pyrexia (3% vs. <1%).
- Thirty-three percent of patients receiving SYLATRON discontinued treatment due to adverse reactions.
- When administering SYLATRON with medications metabolized by CYP2C9 or CYP2D6, the therapeutic effect of these drugs may be altered.
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- It is not known whether the components of SYLATRON are excreted in human 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 treatment with SYLATRON.
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