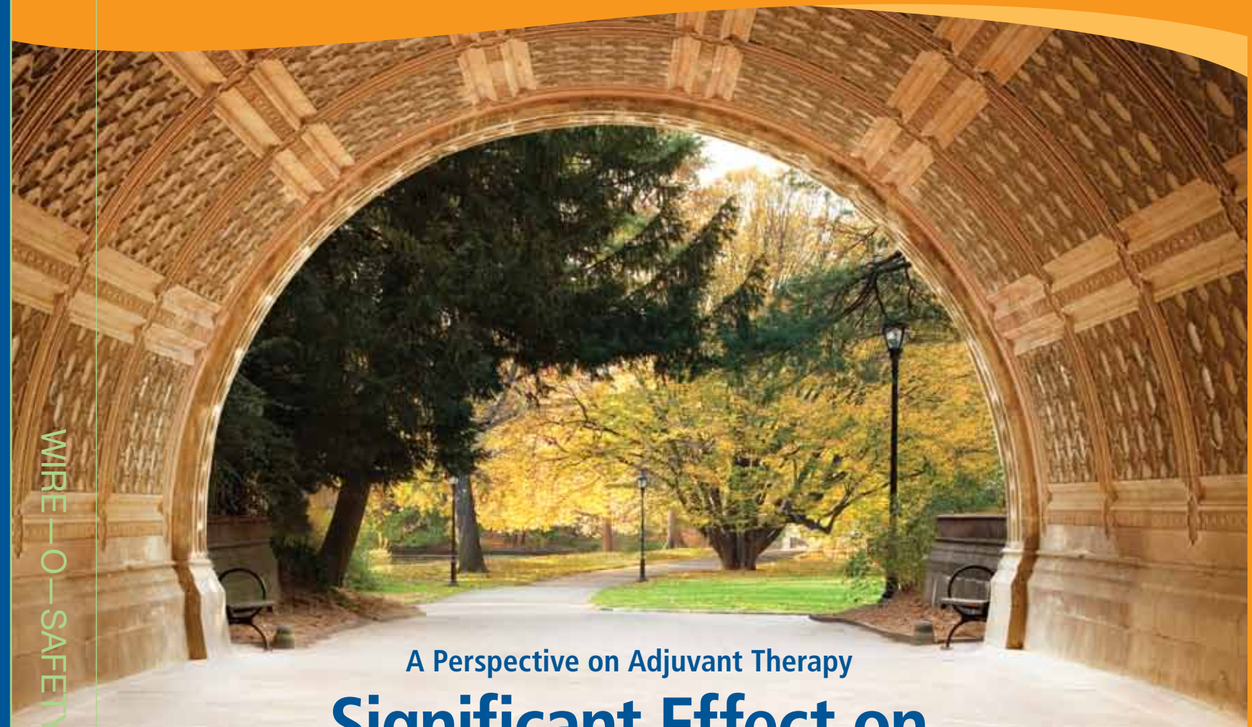
# WHY ADJUVANT THERAPY?

Merck Oncology

WIRE—O—SAFETY—DO_NOT_PRINT

For patients with melanoma
with microscopic or gross nodal involvement



A Perspective on Adjuvant Therapy

# Significant Effect on Relapse-free Survival

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™ (peginterferon alfa-2b) 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.

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

## 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.**

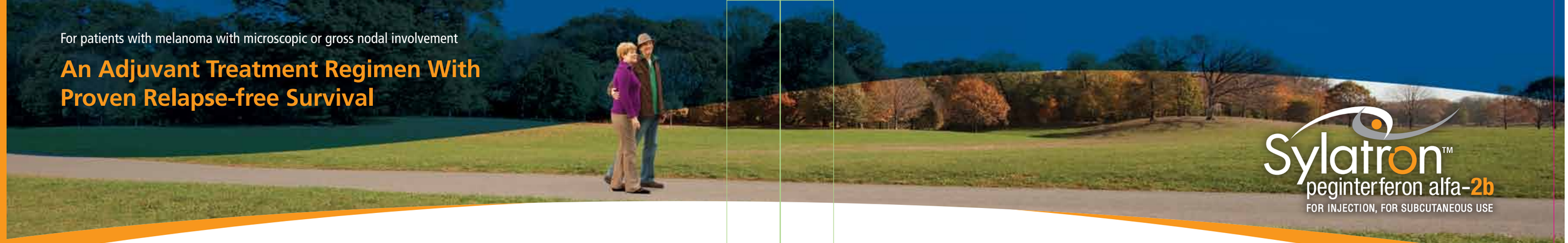
SYLATRON is contraindicated in patients with a history of anaphylaxis to peginterferon alfa-2b or interferon alfa-2b, in patients with autoimmune hepatitis, and in patients with hepatic decompensation (Child-Pugh score >6 [Class B and C]).

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

Sylatron™
peginterferon alfa-2b
FOR INJECTION, FOR SUBCUTANEOUS USE
296 mcg, 444 mcg, 888 mcg

For patients with melanoma with microscopic or gross nodal involvement

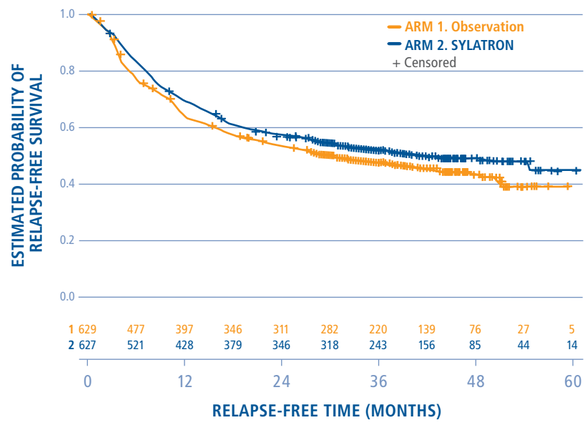
# An Adjuvant Treatment Regimen With Proven Relapse-free Survival



Sylatron™
peginterferon alfa-2b
FOR INJECTION, FOR SUBCUTANEOUS USE

## SYLATRON™ (peginterferon alfa-2b) provides a significant and sustained improvement in relapse-free survival over observation

**Relapse-free Survival in Node-Positive Patients With Malignant Melanoma—ITT Population**




- A randomized, open-label, multicenter study of 1,256 patients with stage III melanoma.
- SYLATRON sustained relapse-free survival over observation throughout the study period.
  - 18% reduction in the risk of relapse (HR = 0.82 [95% CI: 0.71, 0.96], *P*=0.011)
  - 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
- The median duration of therapy at 6 mcg/kg/week was 8.0 weeks and at 3 mcg/kg/week was 14.3 months in the registration trial.
- 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 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 (ITT 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.

RFS=relapse-free survival; CI=confidence interval; ITT=intent-to-treat; HR=hazard ratio; ECOG=Eastern Cooperative Oncology Group.

## 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.





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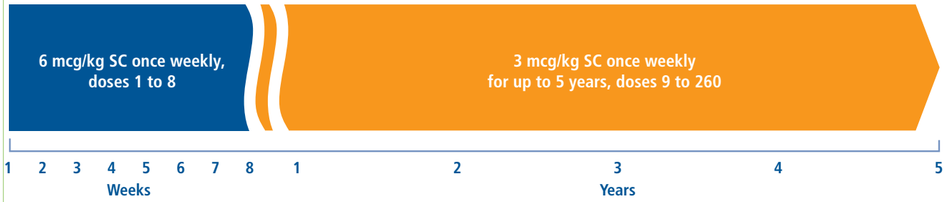
## SYLATRON is a once-weekly subcutaneous injection

**Recommended Treatment Regimen for SYLATRON**



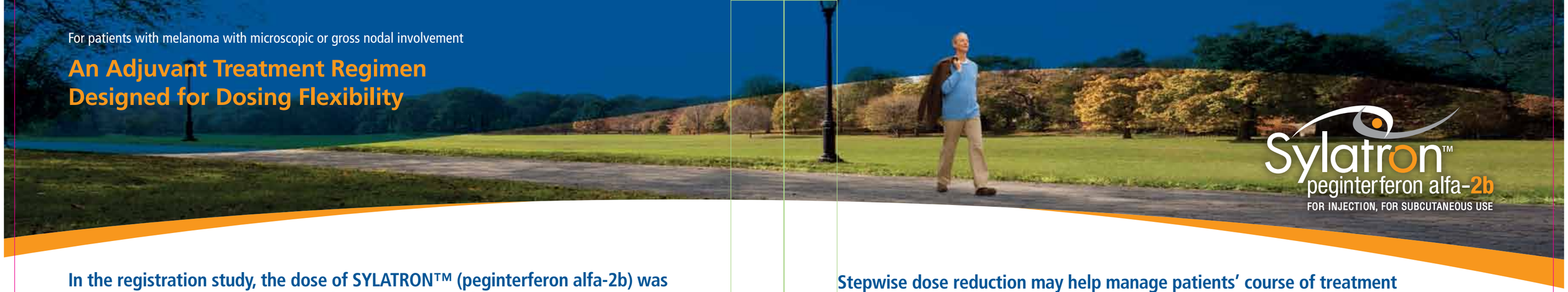

- Premedicate with acetaminophen 500 to 1000 mg orally 30 minutes prior to the first dose of SYLATRON and as needed for subsequent doses.
- Therapy may be administered in the physician's office or at home.
- Single-use vials.
- No refrigeration is required prior to reconstitution.

SC=subcutaneously.

## SELECT IMPORTANT SAFETY INFORMATION

- 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 including 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 treatment with SYLATRON in patients who experience changes in vision. Permanently discontinue SYLATRON in patients who develop new or worsening retinopathy.

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




For patients with melanoma with microscopic or gross nodal involvement

# An Adjuvant Treatment Regimen Designed for Dosing Flexibility

## In the registration study, the dose of SYLATRON™ (peginterferon alfa-2b) was adjusted to maintain an ECOG Performance Status of 0 or 1

### ECOG Performance Status Scale[1]

| GRADE | DESCRIPTION |
|---|---|
| 0 | Fully active; able to carry on all predisease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |
| 5 | Dead |

## Dose-modification guidelines for SYLATRON

- Dose-reduction protocol helps manage both hematologic and nonhematologic toxicities.
- The median duration of therapy at 6 mcg/kg/week was 8.0 weeks and at 3 mcg/kg/week was 14.3 months in the registration trial.

**WITHHOLD DOSE**

**If patient presents with any of the following:**

Hematologic toxicities with:
- Absolute neutrophil count <0.5 x $10^9$/L
- Platelet count <50 x $10^9$/L

Nonhematologic toxicities of:
- ≥Grade 3

Performance Status of:
- ECOG Performance Status (PS) ≥2

**RESUME DOSING AT A MODIFIED DOSE**

**If patient presents with all of the following:**
- Absolute neutrophil count ≥0.5 x $10^9$/L
- Platelet count ≥50 x $10^9$/L
- Nonhematologic toxicity has completely resolved or improved to Grade 1
- ECOG PS 0 or 1

**PERMANENTLY DISCONTINUE SYLATRON**

**If patient presents with any of the following:**
- Persistent or worsening severe neuropsychiatric disorders
- Grade 4 nonhematologic toxicity
- Inability to tolerate a dose of 1 mcg/kg/week
- New or worsening retinopathy

## SELECT IMPORTANT SAFETY INFORMATION

- 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]).





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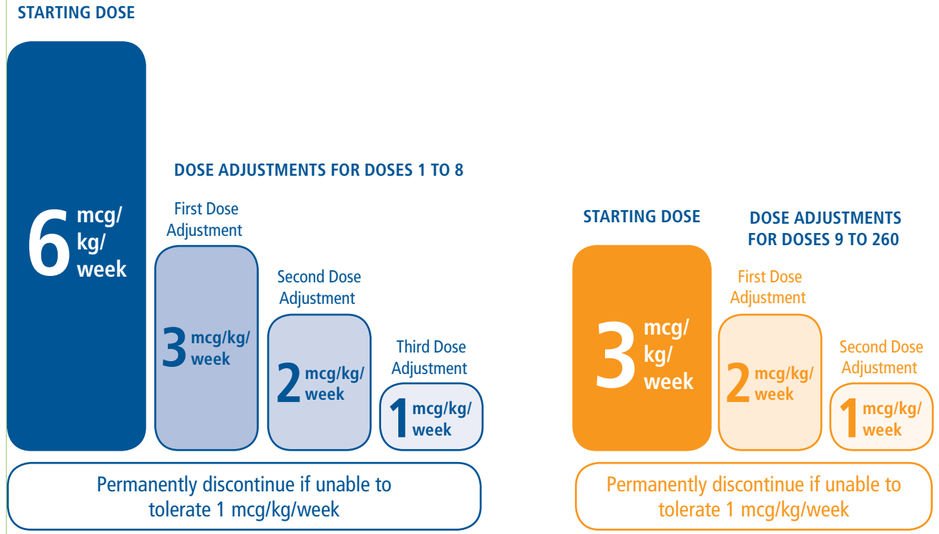
## Stepwise dose reduction may help manage patients' course of treatment




- 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.
- Approximately half (52%) of the patients who continued on therapy after the initial 8 doses underwent dose reductions, and 70% required dose delays (average delay, 2.2 weeks).

## SELECT IMPORTANT SAFETY INFORMATION

- 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.

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

For patients with melanoma with microscopic or gross nodal involvement

# Demonstrated Safety Profile and Recommended Clinical Assessments

Sylatron™
peginterferon alfa-2b
FOR INJECTION, FOR SUBCUTANEOUS USE

## Demonstrated safety profile

**Most Common Adverse Reactions[a] Occurring in Patients With Melanoma Treated With SYLATRON™ (peginterferon alfa-2b) as Compared to Observation**

| ADVERSE REACTION | SYLATRON N=608 | | OBSERVATION N=628 | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 and 4 (%) | All Grades (%) | Grade 3 and 4 (%) |
| Fatigue | 94 | 16 | 41 | 1 |
| ALT or AST increased | 77 | 11 | 26 | 1 |
| Pyrexia | 75 | 4 | 9 | 0 |
| Headache | 70 | 4 | 19 | 1 |
| Anorexia | 69 | 3 | 13 | 0 |
| Myalgia | 68 | 4 | 23 | <1 |
| Nausea | 64 | 3 | 11 | <1 |
| Chills | 63 | 1 | 6 | 0 |
| Injection site reaction | 62 | 1.8 | 0 | 0 |

[a]Adverse reactions were graded using NCI CTCAE, V.2.0.

## SELECT IMPORTANT SAFETY INFORMATION

- The most common adverse reactions in patients treated with SYLATRON vs 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 vs 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.





## Clinical assessments

| ASSESSMENT | | BASELINE | DOSES 1 TO 8 | DOSES 9 TO 260 | AFTER DISCONTINUING THERAPY |
|---|---|---|---|---|---|
| Depression and other serious neuropsychiatric adverse reactions | | | Every 3 weeks | Every 6 months | For 6 months |
| Retinopathy and other serious ocular adverse reactions | | In patients with preexisting retinopathy | Anytime in patients who experience changes in vision | | -na- |
| Hepatic function | Bilirubin | x | Weeks 2 and 8 | Months 2, 3, then every 6 months | -na- |
| | AST/ALT | x | Weeks 2 and 8 | Months 2, 3, then every 6 months | -na- |
| | Alkaline phosphatase | x | Weeks 2 and 8 | Months 2, 3, then every 6 months | -na- |
| | LDH | x | Weeks 2 and 8 | Months 2, 3, then every 6 months | -na- |
| TSH | | Within 4 weeks prior to initiation | -na- | Months 3, 6, then every 6 months | -na- |

## SELECT IMPORTANT SAFETY INFORMATION

- 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.

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

For patients with melanoma with microscopic or gross nodal involvement

# An Adjuvant Treatment Regimen Designed for Dosing Flexibility

Sylatron™
peginterferon alfa-2b
FOR INJECTION, FOR SUBCUTANEOUS USE

## Preparation and administration

| VIAL SIZE | FINAL CONCENTRATION UPON RECONSTITUTION | MAXIMUM DOSE PER VIAL[b] |
|---|---|---|
| | 0.1 mL | 0.5 mL |
| 296 mcg | 40 mcg/0.1 mL | 200 mcg |
| 444 mcg | 60 mcg/0.1 mL | 300 mcg |
| 888 mcg | 120 mcg/0.1 mL | 600 mcg |

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

- SYLATRON™ (peginterferon alfa-2b) is a lyophilized powder in single-use vials that should be reconstituted with the provided 0.7 mL Sterile Water for Injection USP.
- 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.**

## SELECT IMPORTANT SAFETY INFORMATION

- 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.





## SYLATRON is available in 3 strengths

296 mcg
(NDC 0085-1388-01)

444 mcg
(NDC 0085-1287-02)

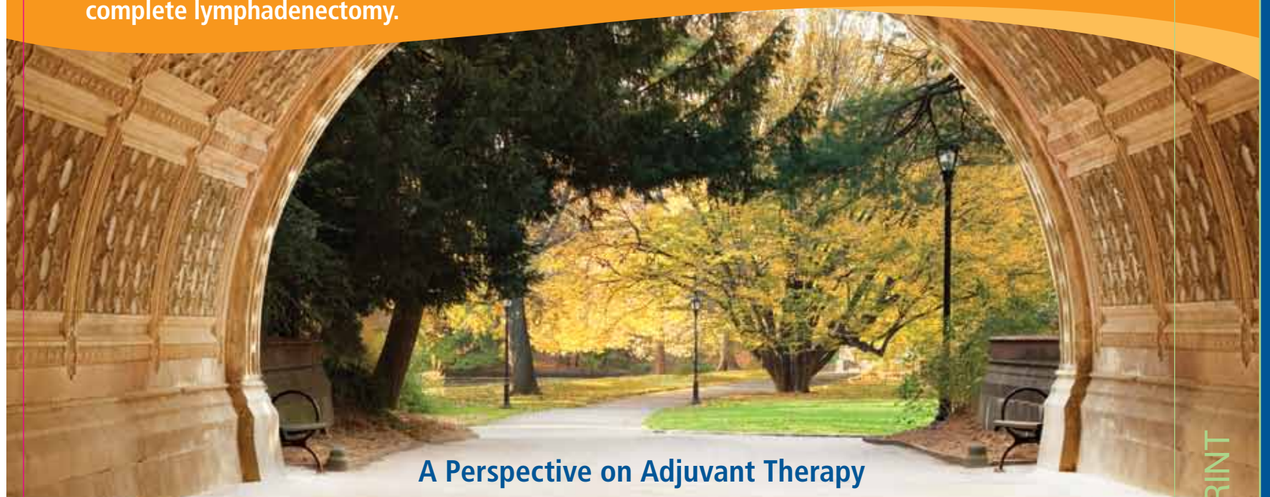
888 mcg
(NDC 0085-1312-01)


## SELECT IMPORTANT SAFETY INFORMATION

- Safety and effectiveness in patients below the age of 18 years have not been established.
- Increase frequency of monitoring for toxicity with SYLATRON in patients with moderate and severe renal impairment.

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

**SYLATRON™ (peginterferon alfa-2b) is indicated for adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.**



### A Perspective on Adjuvant Therapy

# Significant Effect on Relapse-free Survival

- Patients achieved a significant improvement in relapse-free survival.
  - 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.
- Median duration of therapy: 8.0 weeks at the 6 mcg/kg/week dose and 14.3 months at the 3 mcg/kg/week dose.
- Once-weekly subcutaneous administration—in the physician's office or at home.
- In the registration study, the dose of SYLATRON was adjusted to maintain an ECOG Performance Status of 0 or 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.**

**Before prescribing SYLATRON, please read the accompanying 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.

**Reference: 1**. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649–655.

MERCK



Sylatron™
peginterferon alfa-2b
FOR INJECTION, FOR SUBCUTANEOUS USE
296 mcg, 444 mcg, 888 mcg

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WIRE—O—SAFETY—DO_NOT_PRINT

INTRON® A

Interferon Alfa-2b, Recombinant

for Injection, 10 million IU, 18 million IU, 50 million IU

# More Time Without Relapse

INTRON A for Injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery.

**Selected Important Safety Information**

**WARNING**

**Alpha interferons, including INTRON A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping INTRON A therapy.**

INTRON A is contraindicated in patients with hypersensitivity to interferon alpha or any component of the product, autoimmune hepatitis, or decompensated liver disease.

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

INTRON® A
Interferon Alfa-2b, Recombinant
for Injection

# Increased Time to Relapse in High-Risk Patients With Melanoma in Clinical Trials[1–3]

## ECOG 1684 Study Design

- In E1684, 287 patients with cutaneous melanoma were randomly assigned after surgery and lymphadenectomy to receive either 52 weeks of high-dose IFN alfa-2b therapy or observation. Eligible patients had stage IIB or III primary melanoma or had regional nodal recurrence. Randomization was stratified according to clinical and pathologic stage of disease. Patients received induction therapy with IFN alfa-2b at 20 MIU/$m^2$/day IV 5 days per week for 4 weeks, followed by maintenance therapy with IFN alfa-2b at 10 MIU/$m^2$ subcutaneously (SC) 3 times weekly (TIW) for 48 weeks.

## ECOG 1690 Study Design

- Intergroup E1690 was a 3-arm trial comparing high- and low-dose IFN alfa-2b with observation. Patients with stage IIB or primary or recurrent stage III disease were stratified according to AJCC stage of disease and number of involved lymph nodes. They were then randomly assigned to treatment with high-dose IFN alfa-2b (HDI) for 1 year, low-dose IFN alfa-2b (LDI) for 2 years, or observation. HDI consisted of 20 MIU/$m^2$/day IV 5 days per week for 4 weeks, followed by 10 MIU/$m^2$/day SC TIW for 48 weeks. Treatment with LDI was 3 MIU/day SC TIW. Patients were required to have melanoma with definitive surgery with pathologic confirmation of adequate surgical margins within 56 days of initial biopsy, and patients with recurrent regional lymph node disease were required to be randomized within 42 days of lymphadenectomy. In contrast to E1684, patients with T4 (>4 mm thick) primary lesions and no clinical evidence of lymph node metastasis weren't required to undergo lymphadenectomy as high risk was established by the presence of invasion to >4 mm Breslow depth, and because of the absence of any survival benefit of elective lymph node dissection as demonstrated in previous studies.

## ECOG 1694 Study Design

- Intergroup trial E1694 was a prospective randomized study designed to compare the efficacy of high-dose IFN alfa-2b with the investigational vaccine GM2-KLH/QS-21 (GMK) in patients with stage IIB or III melanoma. 880 patients were stratified by sex and number of positive nodes and randomly assigned to treatment with either IFN alfa-2b 20 MU/$m^2$/day IV 5 days per week for 4 weeks, followed by a maintenance dose of 10 MU/$m^2$/day TIW SC for 48 weeks; or to GMK vaccine 1 mL SC on days 1, 8, 15, and 22, and then every 12 weeks for 8 cycles (weeks 12–96).

AJCC= American Joint Committee on Cancer.

# Selected Important Safety Information

- Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases termination of INTRON A therapy. Because of fever and other flulike symptoms associated with INTRON A administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (eg, chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (eg, thrombophlebitis, pulmonary embolism) or severe myelosuppression.





***First FDA-approved agent shown to have proven efficacy in high-risk patients with malignant melanoma***

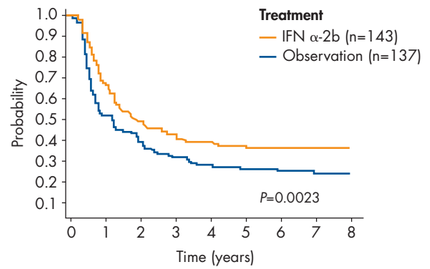
## High-Dose Interferon vs Observation

### ECOG 1684[1] (N=287)

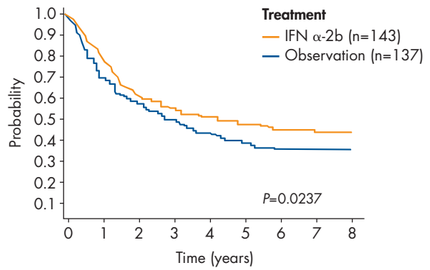
- Randomized controlled trial in resected high-risk patients with cutaneous melanoma evaluating relapse-free survival (RFS) and overall survival (OS).
- Estimated 5-yr RFS 37% vs 26%.
  – 11% absolute improvement
- Estimated 5-yr OS 46% vs 37%.
  – 9% absolute improvement
- Median OS was 3.8 yrs with INTRON® A (interferon alfa-2b, recombinant) vs 2.8 yrs with observation.
- The most common adverse events included constitutional and neuropsychiatric symptoms, along with laboratory findings of myelosuppression and hepatotoxicity.
- Severe toxicities (≥Grade 3) were reported in 67% of patients at some point during therapy with INTRON A; 9% had life-threatening toxicity, and 2 patients died due to hepatic toxicity.
  – Deaths occurred before the predictive value of hepatotoxicity in these patients was fully understood.
- Dose reductions and/or delays for any reason were required in 50% of patients during induction and 48% during maintenance.
- 26% of patients discontinued therapy due to toxicity.[4]

Kirkwood JM, et al. *J Clin Oncol.* 1996;14:7–17.

Relapse-free Survival (Eligible Cases)




Overall Survival (Eligible Cases)






# Selected Important Safety Information

- Cardiovascular Disorders—INTRON A therapy should be used cautiously and closely monitored in patients with a history of cardiovascular disease and/or previous or current arrhythmic disorder. Cardiovascular adverse experiences, which include hypotension, arrhythmia, or tachycardia, and rarely, cardiomyopathy and myocardial infarction, have been observed in some INTRON A–treated patients. Some patients with these adverse events had no history of cardiovascular disease. Hypotension may occur during INTRON A administration or up to 2 days posttherapy.
- Cerebrovascular Disorders—Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with INTRON A.

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

INTRON® A
Interferon Alfa-2b, Recombinant
for Injection

# Increased Time to Relapse in High-Risk Patients With Melanoma in Clinical Trials[1–3]

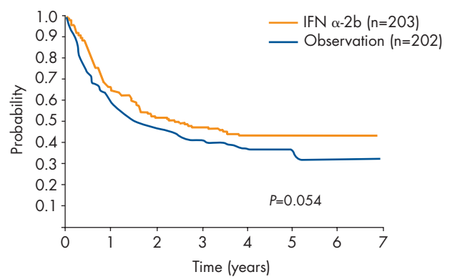
## High-Dose Interferon vs Observation

### Intergroup E1690[2] (N=642)

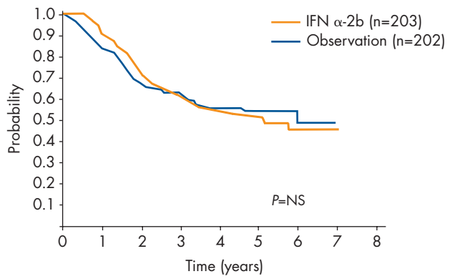
- Randomized 3-arm trial in high-risk patients with cutaneous melanoma evaluating RFS and OS.
- Kaplan-Meier estimated 5-yr RFS 44% vs 35% for the ITT analysis (*P*=0.03 by Cox model analysis).
  - 9% absolute improvement
- The HR for RFS for INTRON A vs observation was 1.28 (*P*=0.054 by ITT analysis).
- No OS benefit was demonstrated in this study.
- The majority of adverse events were Grade 3.
- Grade 3 adverse events occurring in ≥5% of patients receiving INTRON A included granulocytopenia, liver toxicity, fatigue, neuroclinical, myalgia, leukopenia, nausea, neuropsychiatric, neuromotor, and vomiting.
- Dose reductions or delays in receiving INTRON A for any reason were required in 58% of patients during induction and 59% during maintenance.
  - Trial used a 2-step dose-reduction protocol
- No treatment-related deaths occurred.
- 13% of patients discontinued therapy due to toxicity.[4]

Kirkwood JM, et al. *J Clin Oncol*. 2000;18:2444–2458.
ITT=intent-to-treat; HR=hazard ratio.

Relapse-free Survival (Eligible Cases)




Overall Survival (Eligible Cases)






## Selected Important Safety Information

- Neuropsychiatric Disorders—DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES, HOMICIDAL IDEATION, AND AGGRESSIVE BEHAVIOR SOMETIMES DIRECTED TOWARDS OTHERS, HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALPHA INTERFERONS, INCLUDING INTRON A THERAPY. If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6-month follow-up period. INTRON A should be used with caution in patients with a history of psychiatric disorders. INTRON A therapy should be discontinued for any patient developing a severe psychiatric disorder during treatment. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that treatment with INTRON A be discontinued, and the patient followed with psychiatric intervention as appropriate. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients during treatment and off-therapy follow-up. Cases of encephalopathy have also been observed in some patients, usually elderly, treated with higher doses of INTRON A.





***First FDA-approved agent shown to have proven efficacy in high-risk patients with malignant melanoma***

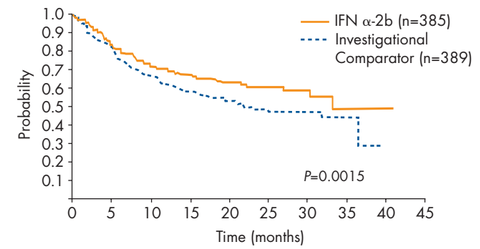
## High-Dose Interferon vs Investigational Comparator

### Intergroup E1694[3] (N=880)

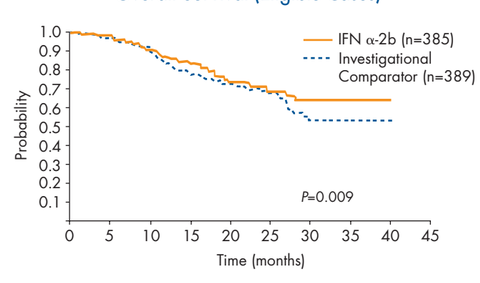
- Randomized trial in high-risk patients with cutaneous melanoma evaluating RFS and OS.
- Median follow-up: 1.3 yrs.
- 47% improvement in RFS for eligible cases (*P*=0.0015).
  - The HR for RFS for INTRON® A (interferon alfa-2b, recombinant) vs the investigational comparator was 1.47.
- 52% improvement in OS for eligible cases (*P*=0.009).
  - The HR for OS for INTRON A vs the investigational comparator was 1.52.
- Estimated 2-yr OS rates: 78% vs 73%.
  - 5% absolute improvement
- Trial was closed early at interim analysis when comparator was found to be inferior to high-dose IFN.
- The majority of adverse events were Grade 3.
- Grade 3 adverse events occurring in ≥5% of patients receiving INTRON A included granulocytopenia, liver toxicity, fatigue, neuroclinical, neuropsychiatric, and neuromotor events.
- Dose reductions or delays in therapy with INTRON A for any reason were required in 33% of patients during induction and 38% during maintenance.
  - Trial used a 2-step dose-reduction protocol
- No treatment-related deaths occurred.
- 10% of patients discontinued therapy due to toxicity.[4]

Kirkwood JM, et al. *J Clin Oncol*. 2001;19:2370–2380.

Relapse-free Survival (Eligible Cases)




Overall Survival (Eligible Cases)






## Selected Important Safety Information

- Bone Marrow Toxicity—INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including aplastic anemia. INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/L) or platelet counts ($<25 \times 10^9$/L).

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

INTRON® A
Interferon Alfa-2b, Recombinant
for Injection

## Recommended Treatment Regimen

| Treatment Regimen of INTRON A for Malignant Melanoma |
|---|
| **Induction:** 20 MIU/$m^2$ intravenously 5 consecutive days per week for 4 weeks |
| **Maintenance:** 10 MIU/$m^2$ as a subcutaneous injection 3 times per week for 48 weeks |

## Dose Modification for INTRON A

Dosage reductions may be needed during treatment as a result of side effects that may develop, including depression or a change in laboratory values. Therapy with INTRON A should be discontinued for any patient developing severe depression or other psychiatric disorder during treatment. Please see the full Prescribing Information for a complete discussion of when to discontinue therapy with INTRON A.

**Dose Modifications of INTRON A for Malignant Melanoma**

| Laboratory Values | Guidelines for Dose Modification and Discontinuation of INTRON A |
|---|---|
| Granulocytes/neutrophils drop to <500/$mm^3$ | Temporarily discontinue treatment until the adverse reaction abates. Restart INTRON A at 50% of the previous dose. |
| Granulocytes/neutrophils drop to <250/$mm^3$ | INTRON A should be permanently discontinued. |
| SGPT/SGOT (ALT/AST) rises to >5x upper limit of normal | Temporarily discontinue treatment until the adverse reaction abates. Restart INTRON A at 50% of the previous dose. |
| SGPT/SGOT (ALT/AST) rises to >10x upper limit of normal | INTRON A should be permanently discontinued. |

SGPT/SGOT=serum glutamic-pyruvic transaminase/serum glutamic-oxaloacetic transaminase; ALT/AST=alanine aminotransferase/aspartate aminotransferase.

## Selected Important Safety Information

- Ophthalmologic Disorders—Decrease or loss of vision, retinopathy including 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 INTRON A or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders should receive periodic ophthalmologic exams during INTRON A treatment. INTRON A treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.
- Endocrine Disorders—Infrequently, patients receiving INTRON A therapy developed thyroid abnormalities, either hypothyroid or hyperthyroid, and diabetes mellitus. Patients with preexisting thyroid abnormalities or diabetes mellitus who cannot be effectively treated by medication should not be treated with INTRON A. Prior to initiation of INTRON A therapy, serum TSH should be evaluated. INTRON A therapy should be discontinued for patients developing thyroid abnormalities or diabetes mellitus during treatment.



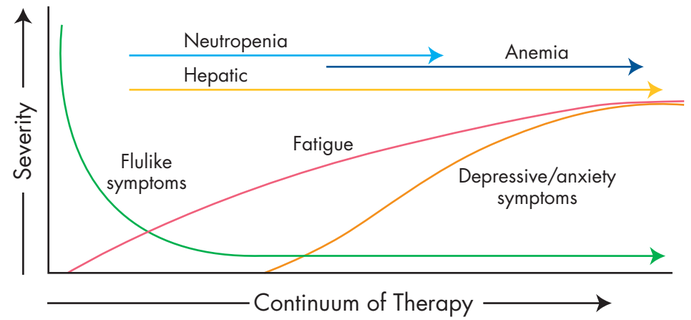


*First FDA-approved agent shown to have proven efficacy in high-risk patients with malignant melanoma*

## Management of Therapy With High-Dose INTRON® A (interferon alfa-2b, recombinant)

### Appropriate Side Effect Monitoring Is Important for Patients on INTRON A[5]

**Occurrence of Selected Side Effects During Therapy With INTRON A[4]**




Adapted from Hauschild A, et al. *Cancer.* 2008;112:982–994.

- Data from 3 clinical trials showed[1–4]:
  - The most common severe or life-threatening adverse events in patients treated with INTRON A were fatigue, cytopenia, fever/chills, myalgia, anorexia, nausea/vomiting, liver toxicity, and neurologic symptoms.

## Selected Important Safety Information

- Gastrointestinal Disorders—Hepatotoxicity, including fatality, has been observed in patients treated with INTRON A. Patients developing liver function abnormalities during treatment should be monitored, and if appropriate, INTRON A treatment should be discontinued.
- Pulmonary Disorders—Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by INTRON A or other alpha interferons. Recurrence of respiratory failure has been observed with interferon rechallenge. Any patient developing fever, cough, dyspnea, or other respiratory symptoms should have a chest X-ray and, if there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored and, if appropriate, INTRON A treatment should be discontinued.

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

INTRON® A
Interferon Alfa-2b, Recombinant
for Injection

# Help Your Patients Manage Common Side Effects

### Flulike symptoms

- Common at the start of therapy.
- Acetaminophen may be administered at the time of injection.
- To enhance the tolerability of INTRON A, injections should be administered in the evening when possible.

### Fatigue[5]

- Adequate hydration is important; fluid requirements vary based on comorbid conditions such as diabetes.
- Encourage patients to conserve energy and pace themselves.
- Encourage patients to delegate tasks whenever desirable or possible.
- Suggest patients prioritize activities and plan important events for days when energy level is high.

## Selected Important Safety Information

- Autoimmune Disorders—Rare cases of autoimmune diseases including thrombocytopenia, vasculitis, Raynaud's phenomenon, rheumatoid arthritis, lupus erythematosus, and rhabdomyolysis have been observed in patients treated with INTRON A. In very rare cases the event resulted in fatality. Any patient developing an autoimmune disorder during treatment should be closely monitored and, if appropriate, INTRON A treatment should be discontinued.
- Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely in INTRON A–treated patients; if such an acute reaction develops, the drug should be discontinued immediately and appropriate medical therapy instituted. There have been reports of INTRON A exacerbating preexisting psoriasis and sarcoidosis as well as development of new sarcoidosis.





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***First FDA-approved agent shown to have proven efficacy in high-risk patients with malignant melanoma***

### Depression

- Occurs in up to 40% of patients.[5]
- Must assess depression before and during treatment (BDI/CES-D).[5]
- Ask patients if they experience any mood changes or suicidal/homicidal thoughts.[5]
- Consider formal psychiatric consult, antidepressants.[5]
- If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6-month follow-up period.
- INTRON® A (interferon alfa-2b, recombinant) should be used with caution in patients with a history of psychiatric disorders. INTRON A should be discontinued for any patient developing a severe psychiatric disorder during treatment.
- If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior toward others is identified, it is recommended that treatment with INTRON A be discontinued and the patient followed with psychiatric intervention as appropriate.

BDI=Beck Depression Inventory; CES-D=Center for Epidemiological Studies Depression Scale.

## Selected Important Safety Information

- Triglycerides—Elevated triglyceride levels (which may result in pancreatitis) have been observed in patients treated with INTRON A. Discontinuation of INTRON A therapy should be considered for patients with persistently elevated triglycerides associated with symptoms of potential pancreatitis.
- In clinical trials, adverse reactions, classified as severe or life threatening, were recorded in 66% and 14% of INTRON A–treated patients, respectively. Severe adverse reactions recorded in >10% of INTRON A–treated patients included neutropenia/leukopenia, fatigue, fever, myalgia, headache, chills, and increased SGOT. Grade 4 fatigue was recorded in 4% and Grade 4 depression in 2% of INTRON A–treated patients.
- The most frequently reported adverse reaction was fatigue, which was observed in 96% of patients. Other adverse reactions recorded in >20% included neutropenia, fever, myalgia, anorexia, vomiting/nausea, increased SGOT, headache, chills, depression, diarrhea, alopecia, altered taste sensation, dizziness/vertigo, and anemia.

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

INTRON® A

Interferon Alfa-2b, Recombinant

for Injection, 10 million IU, 18 million IU, 50 million IU

# More Time Without Relapse

## in High-Risk Malignant Melanoma

- The first FDA-approved therapy for the adjuvant treatment of high-risk patients with malignant melanoma
- Helps prolong relapse-free[1–3] and overall survival[1,3]
- Proven efficacy in independent US cooperative group trials[1–3]

INTRON A for Injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery.

### Selected Important Safety Information

**WARNING**

**Alpha interferons, including INTRON A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping INTRON A therapy.**

**References: 1.** Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol.* 1996;14:7–17. **2.** Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup Trial E1690/S9111/C9190. *J Clin Oncol.* 2000;18:2444–2458. **3.** Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of Intergroup Trial E1694/S9512/C509801. *J Clin Oncol.* 2001;19:2370–2380. **4.** Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon-α-2b side effects in patients receiving adjuvant treatment for melanoma. *Cancer.* 2008;112:982–984. **5.** Kirkwood JM, Bender C, Agarwala S, et al. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol.* 2002;20:3703–3718.

**Before prescribing INTRON A, please read the accompanying Prescribing Information, including the Boxed Warning, about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**

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

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