Rebif® (interferon beta-1a) subcutaneous injection

NEED TO DE-ESCALATE AN RMS PATIENT TO A DIFFERENT THERAPY?

Consider Rebif®

INDICATION

For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

Use Rebif with caution in patients with depression, a common condition in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Please see Important Safety Information throughout and on page 10, as well as Rebif Prescribing Information and Medication Guide.

When de-escalating an RMS patient, which of these key factors do you consider?

TREATMENT DECISIONS MUST BE DETERMINED ON A CASE-BY-CASE BASIS[1]

According to the 2018 American Academy of Neurology (AAN) practice guideline,* some key considerations when switching DMTs include:[2]

- Risk of opportunistic infections, including progressive multifocal leukoencephalopathy (PML)
- Safety and tolerability profile
- Changes in disease activity

*Practice guideline: Disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN. March 6, 2018.

DMT: disease-modifying therapy.

IMPORTANT SAFETY INFORMATION (cont'd)

There have been rare reports of severe liver injury, including some cases of hepatic failure requiring liver transplantation, in patients taking Rebif. Consider the potential for hepatic injury when Rebif is used in combination with other products associated with hepatotoxicity. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

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RISK OF OPPORTUNISTIC INFECTION[2,3]

- Different treatment options may be preferred for patients who are at higher risk for serious infections, including PML

SAFETY PROFILE AND TOLERABILITY[1-3]

- The safety profile and clinical experience of a switch DMT
- The tolerability of a switch DMT

CHANGES IN DISEASE ACTIVITY[2]

- MRI activity
- Relapses
- Disability progression

Consider the efficacy and safety profile of Rebif® when talking to your patients about switching their treatment[4]

IMPORTANT SAFETY INFORMATION (cont'd)

Anaphylaxis and other allergic reactions (some severe) have been reported. Discontinue Rebif if anaphylaxis occurs.

In controlled clinical trials, injection site reactions occurred more frequently in Rebif-treated patients than in placebo-treated and Avonex-treated patients.

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Rebif® demonstarted significant reductions in relapses in patients with a range of disability[5-7]

DEMONSTRATED REDUCTION IN THE MEAN NUMBER OF RELAPSES vs PLACEBO AT 2 YEARS[5,6]

TOTAL (0 TO 5.0 EDSS) COHORT

32%

Rebif 44 mcg: 1.73 (n=184) vs placebo: 2.56 (n=187), *P*<0.0001

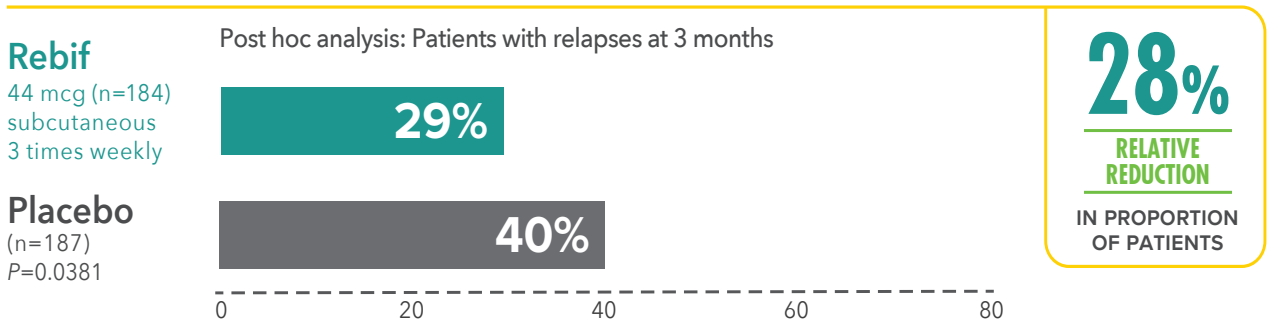
HIGHER BASELINE (>3.5 TO 5.0 EDSS) COHORT

60%

Rebif 44 mcg: 1.22 (n=31) vs placebo: 3.07 (n=28), *P*<0.0002

FEWER PATIENTS HAD A RELAPSE AT 3 MONTHS WITH REBIF® vs PLACEBO[7]

TOTAL PATIENT COHORT (BASELINE EDSS 0 TO 5.0)



THE RATE OF SERIOUS ADVERSE EVENTS IN PATIENTS WITH EDSS 3.5 TO 5.0 (REGARDLESS OF CAUSALITY) WAS 20% vs 11.3% FOR THE TOTAL PATIENT COHORT (EDSS 0 TO 5.0).[6]

EDSS: Expanded Disability Status Scale.

IMPORTANT SAFETY INFORMATION (cont'd)

Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting with the use of Rebif. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, change injection site or discontinue Rebif until skin lesions are healed. Some cases of injection site necrosis required treatment with intravenous antibiotics and surgical intervention (debridement and skin grafting). Some cases of injection site abscesses and cellulitis required treatment with hospitalization for surgical drainage and intravenous antibiotics. Rotate site of injection with each dose to minimize likelihood of severe injection site reactions, including necrosis or localized infection.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Monitor patients for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

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REGARDLESS OF AGE, REBIF® DEMONSTRATED A REDUCTION IN ARR* AT 2 YEARS[4,5,8]

ARR AT 2 YEARS IN AGES 18-55 vs PLACEBO (BASELINE EDSS 0 TO 5.0)

33%

AGE<40

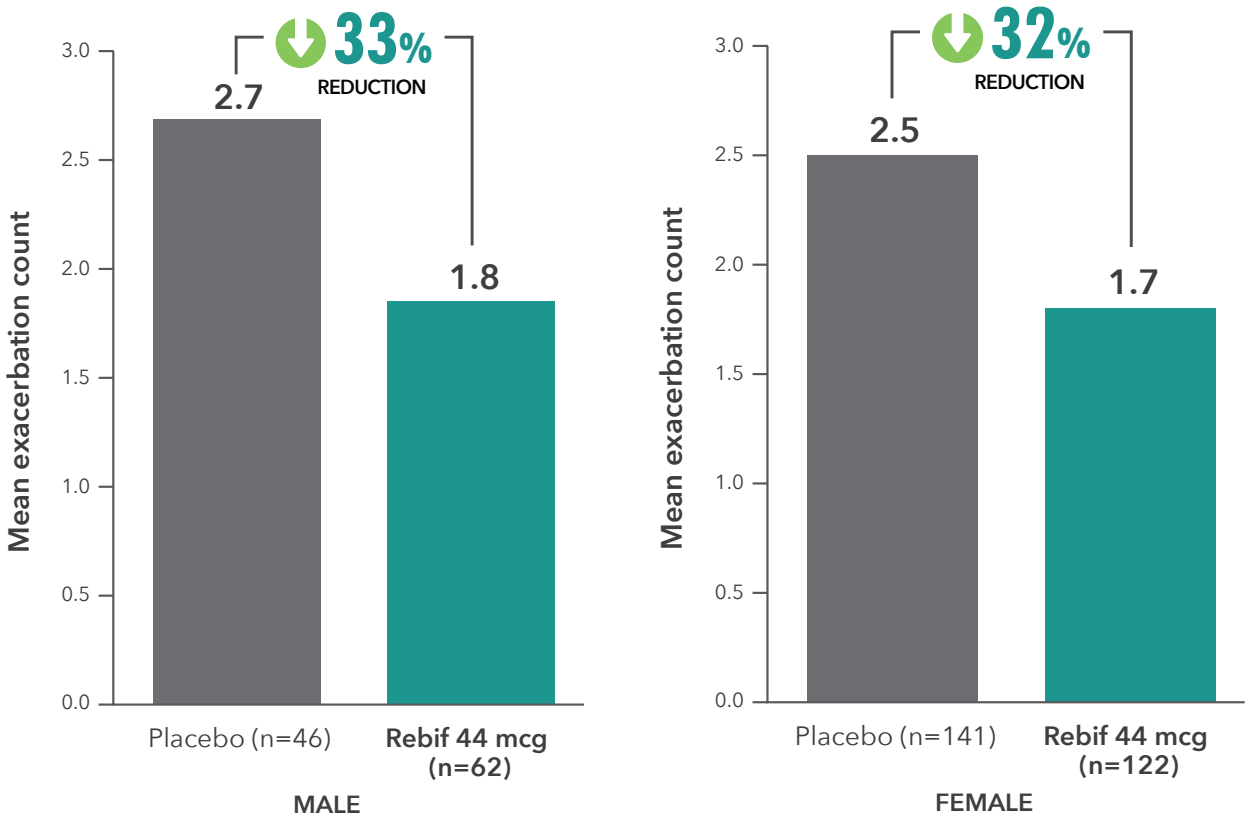
Post hoc analysis ages 18-39 (n=129) vs placebo (n=135), HR=0.67, CI: (0.57-0.79), *P*<0.001

33%

AGE≥40

Post hoc analysis ages 40-55 (n=55) vs placebo (n=52), HR=0.67, CI: (0.51-0.87), *P*<0.003

REGARDLESS OF GENDER, REBIF DEMONSTRATED A REDUCTION IN RELAPSE AT 2 YEARS[6]



*ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; HR: hazard ratio.

PRISMS STUDY DESIGN

Prevention of **R**elapses and Disability by **I**nterferon β-1a **S**ubcutaneously in **M**ultiple **S**clerosis (**PRISMS**) was a double-blind, placebo-controlled study conducted over 2 years. Patients were randomly assigned Rebif 44 mcg (n=184), Rebif 22 mcg (n=189), or placebo (n=187), given 3 times weekly by subcutaneous injection. Outcomes measured included relapse rate, disability, MRI, safety, and antigenicity. Neurological assessments were conducted every 3 months.[5]

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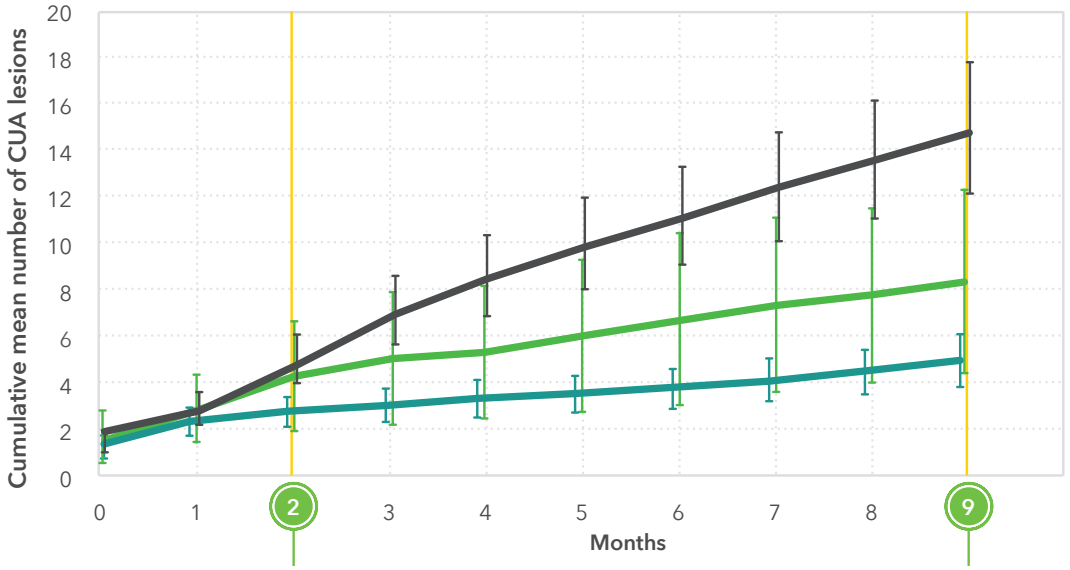
Rebif® demonstrated a significant reduction in MRI lesions[4,6,9]

PATIENTS ON REBIF SHOWED A 78% REDUCTION IN NUMBER OF T2-ACTIVE LESIONS vs PLACEBO AFTER 2 YEARS[4,9]*

Median number of T2-active lesions per patient per scan was 0.5 for Rebif 44 mcg (n=171) vs 2.25 for placebo (n=172); *P*<0.0001.

SIGNIFICANT CUA LESION REDUCTION SEEN AS EARLY AS 2 MONTHS AND PERSISTED UP TO 9 MONTHS[6†‡§]

MONTHLY SCANS–MEAN NUMBER OF CUA LESIONS OVER TIME



42% RELATIVE REDUCTION

Post hoc analysis:
Rebif 44 mcg (n=67): 32% vs placebo (n=66): 55%, *P*=0.0008

REDUCTION IN PERCENT COMBINED ACTIVE SCANS PER PATIENT†‡§

62% RELATIVE REDUCTION

Prespecified endpoint:
Rebif 44 mcg (n=68): 19% vs placebo (n=66): 50%, *P*<0.0001

CUA: combined unique active.
*Based on comparisons from rank-based ANOVA.[6]
†From a subgroup of 205 patients who underwent monthly MRI scans for the first 9 months, intent-to-treat population had biannual scans.[9]
‡Analysis of the subgroup of patients undergoing PD/T2 and T1-Gd+ MRI scans at prestudy day 1, and monthly for the first 9 months of treatment based on ANOVA on the ranks taking center and number of active lesions at baseline into account.[6]
§Proportion of scans per patient per treatment group with new activity, including new, enlarging, recurrent PD/T2, or enhancing T1 lesions.[9]

IMPORTANT SAFETY INFORMATION (cont'd)

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur and manage as clinically indicated.

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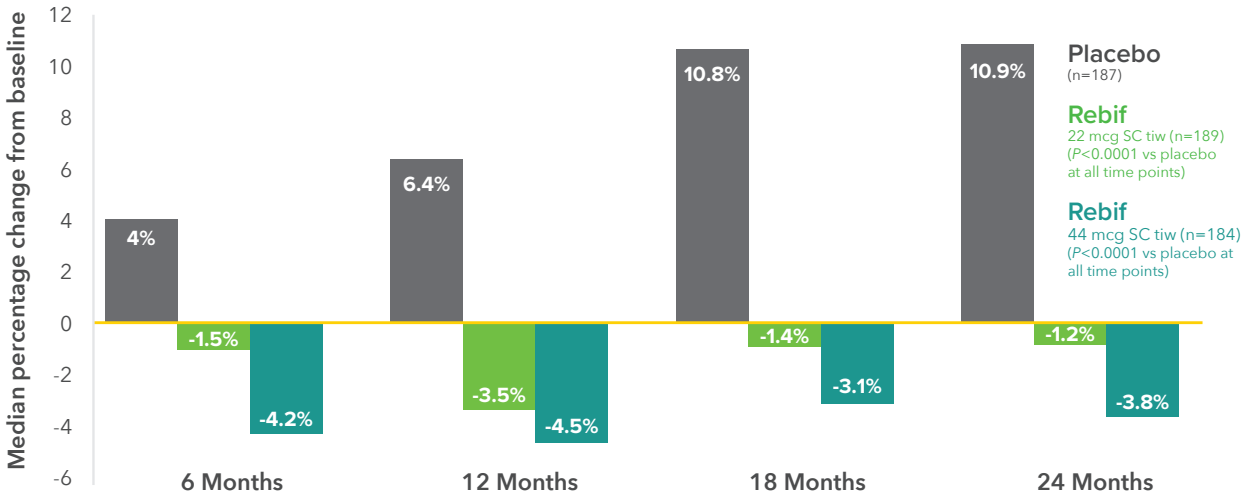
PD/T2 LESION LOAD DECREASED SIGNIFICANTLY COMPARED WITH PLACEBO[5,9]

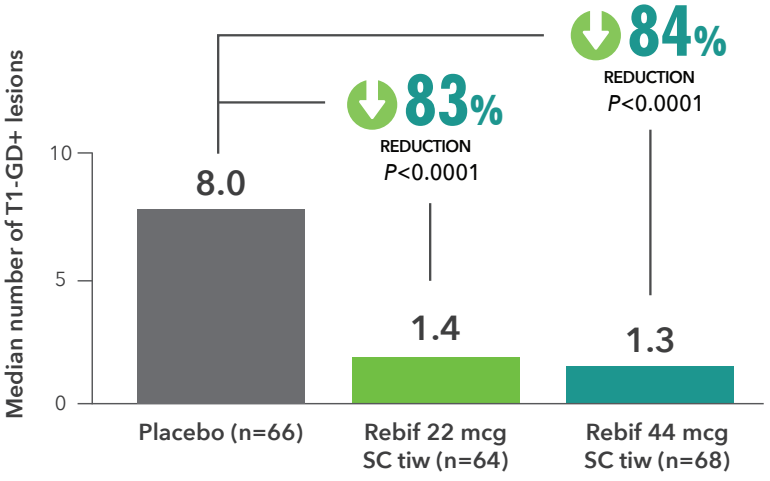
DECREASED PD/T2 LESION LOAD: BIANNUAL SCANS[9]



N values: at 6 months, placebo (n=182), Rebif 22 mcg (n=182), Rebif 44 mcg (n=182); at 12 months, placebo (n=179), Rebif 22 mcg (n=180), Rebif 44 mcg (n=180); at 18 months, placebo (n=176), Rebif 22 mcg (n=177), Rebif 44 mcg (n=172); and at 24 months, placebo (n=172), Rebif 22 mcg (n=171), Rebif 44 mcg (n=171).[9]
Lesion load is defined as the total area of lesions in the brain measured in mm.[2,6]
PD: proton density; SC: subcutaneous; tiw: 3 times weekly.

T1-GD+ LESIONS SHOWED A SIGNIFICANT REDUCTION COMPARED WITH PLACEBO[9]

SIGNIFICANT REDUCTIONS IN T1-GD+ LESIONS AT 9 MONTHS[‖¶]



‖From a subgroup of 205 patients who underwent monthly MRI scans for the first 9 months, intent-to-treat population had biannual scans.

¶Analysis of the subgroup of patients undergoing PD/T2 and T1-Gd+ MRI scans at prestudy screening, study day 1, and monthly for the first 9 months of treatment based on ANOVA on the ranks taking center and number of active lesions at baseline into account.

T1-Gd+: T1-weighted gadolinium-enhancing.

IMPORTANT SAFETY INFORMATION (cont'd)

Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports. Monitor for seizures when administering Rebif to patients, particularly those with pre-existing seizure disorders.

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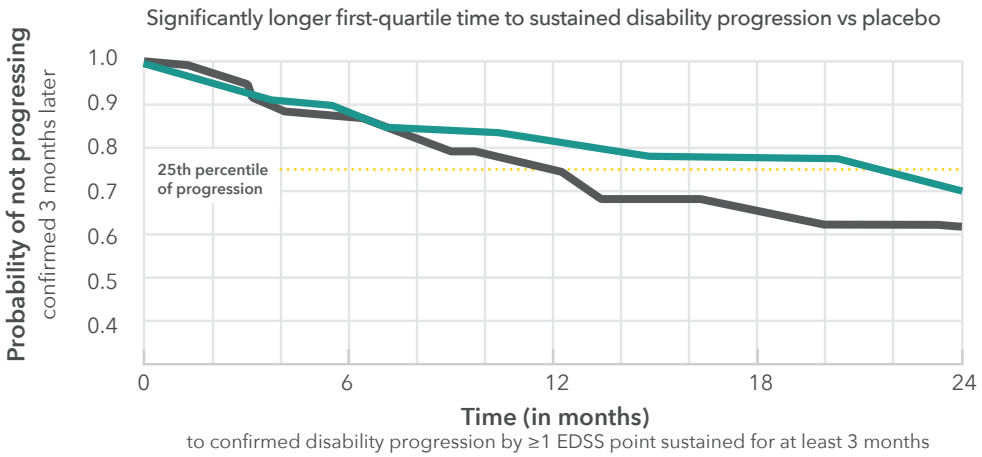
Significant delay in disability progression vs placebo in patients with a range of disability[5,6]

TOTAL PATIENT COHORT (BASELINE EDSS 0 TO 5.0)

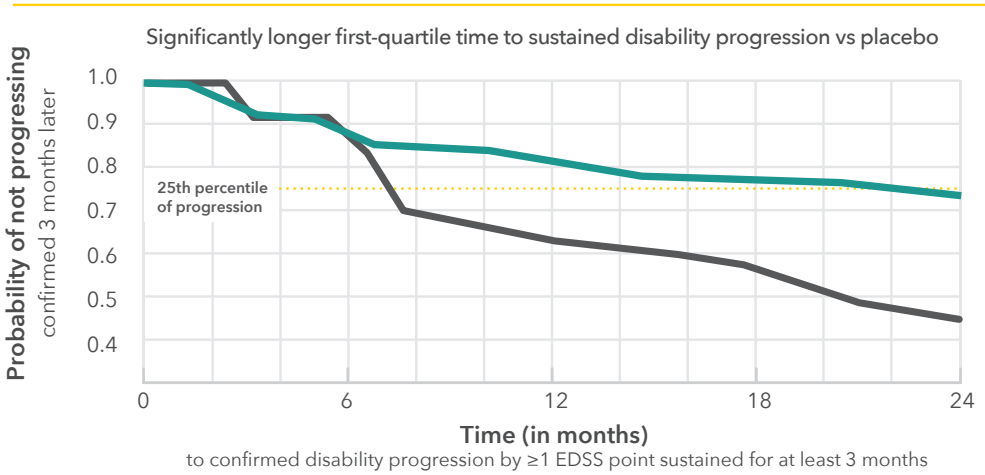


≈2× LONGER TO CDP*

Rebif®
44 mcg (n=184)
subcutaneous 3 times weekly
21.3 months

Placebo
(n=187) 11.9 months
P=0.0136 with hazard ratio 0.62

HIGHER EDSS COHORT (BASELINE EDSS >3.5 TO 5.0)



≈3× LONGER TO CDP*

Rebif
44 mcg (n=31)
subcutaneous 3 times weekly
21.3 months

Placebo
(n=28) 7.3 months
P<0.05 with hazard ratio 0.42

In time to confirmed disability progression (CDP), a statistically significant difference was seen between Rebif 22 mcg and placebo in the total patient cohort (0 to 5.0) but was not seen in the higher baseline EDSS cohort (>3.5 to 5.0).

The rate of serious adverse events in patients with EDSS >3.5 to 5.0 (regardless of causality) was 20% vs 11.3% for the total patient cohort (EDSS 0 to 5.0).

**Progression of disability* was defined as an increase of at least 1 point in the Expanded Disability Status Scale (EDSS), sustained for at least 3 months.

IMPORTANT SAFETY INFORMATION (cont'd)

New or worsening thyroid abnormalities have developed in some patients treated with Rebif. Thyroid function tests are recommended every 6 months in patients with history of thyroid dysfunction or as clinically indicated.

The most common side effects with Rebif are injection-site disorders, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

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References

1. Freedman M, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci*. 2013;40(3):307-323.
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8. Freedman MS, Brod S, Wray S, et al. Post hoc analysis to evaluate the effects of subcutaneous interferon beta-1a in subgroups of patients from the PRISMS study with early onset versus late onset disease. Poster presented at: ECTRIMS 2019; 11-13 September; Stocholm, Sweden.
9. Li DKB, Paty DW; UBC MS/MRI Analysis Research Group, PRISMS Study Group. Magnetic resonance imaging results of the PRISMS trial: a randomized double-blind, placebo-controlled study of interferon-β1a in relapsing-remitting multiple sclerosis. *Ann Neurol*. 1999;46(2):197-206.

IMPORTANT SAFETY INFORMATION (cont'd)

Epidemiological data do not suggest a clear relationship between interferon beta use and major congenital malformations, but interferon beta may cause fetal harm based on animal studies. Data from a large human population-based cohort study, as well as other published studies over several decades, have not identified an increased risk of major birth defects with exposure to interferon beta products during early pregnancy. Findings regarding a potential risk for low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent.

Please see Rebif Prescribing Information and Medication Guide.

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Indication and Important Safety Information

INDICATION

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Anaphylaxis and other allergic reactions (some severe) have been reported. Discontinue Rebif if anaphylaxis occurs.

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Please see the full Rebif Prescribing Information and Medication Guide by clicking the tabs above.

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Indication and Important Safety Information (cont'd)

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