Rebif® (interferon beta-1a) subcutaneous injection

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

CONSIDER REBIF®

INDICATION

Rebif® is indicated 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.

Rebif® should be used with caution in patients with depression, a condition that is common 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 additional Important Safety Information inside and linked Rebif® full Prescribing Information

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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)

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

Please see additional Important Safety Information on page 9.

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 as a rare complication of Rebif. 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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Please see additional Important Safety Information on page 9.

REBIF® DEMONSTRATED 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

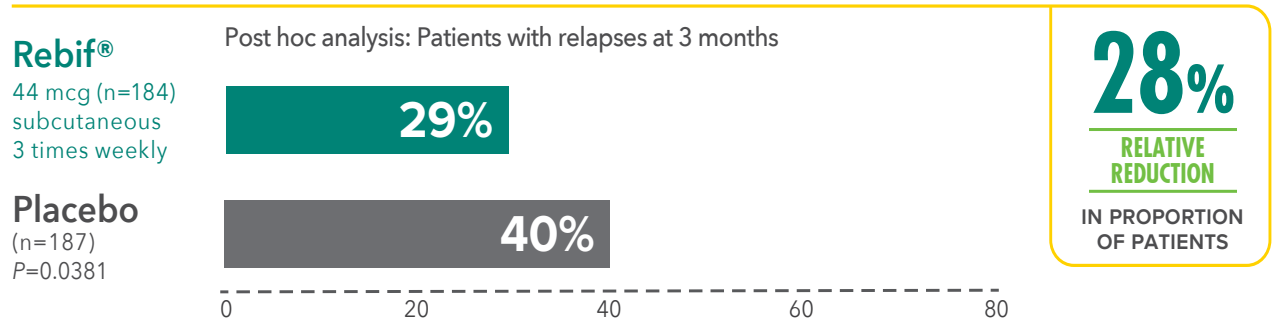
HIGHER BASELINE (>3.5 TO 5.0 EDSS) COHORT

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. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

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-treated and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Please see additional Important Safety Information on page 9.

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)

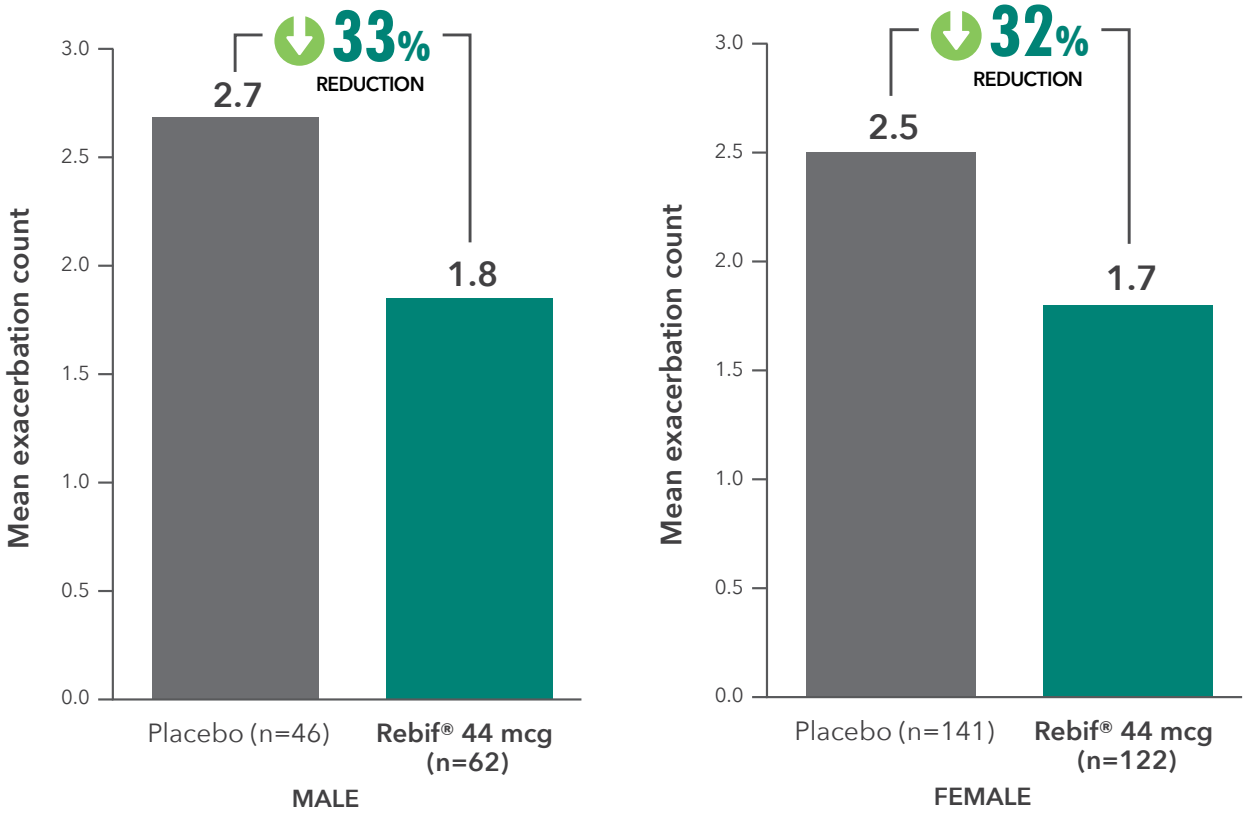
33%
AGE<40

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

33%
AGE≥40

Post hoc analysis ages 40-55 (n=55), 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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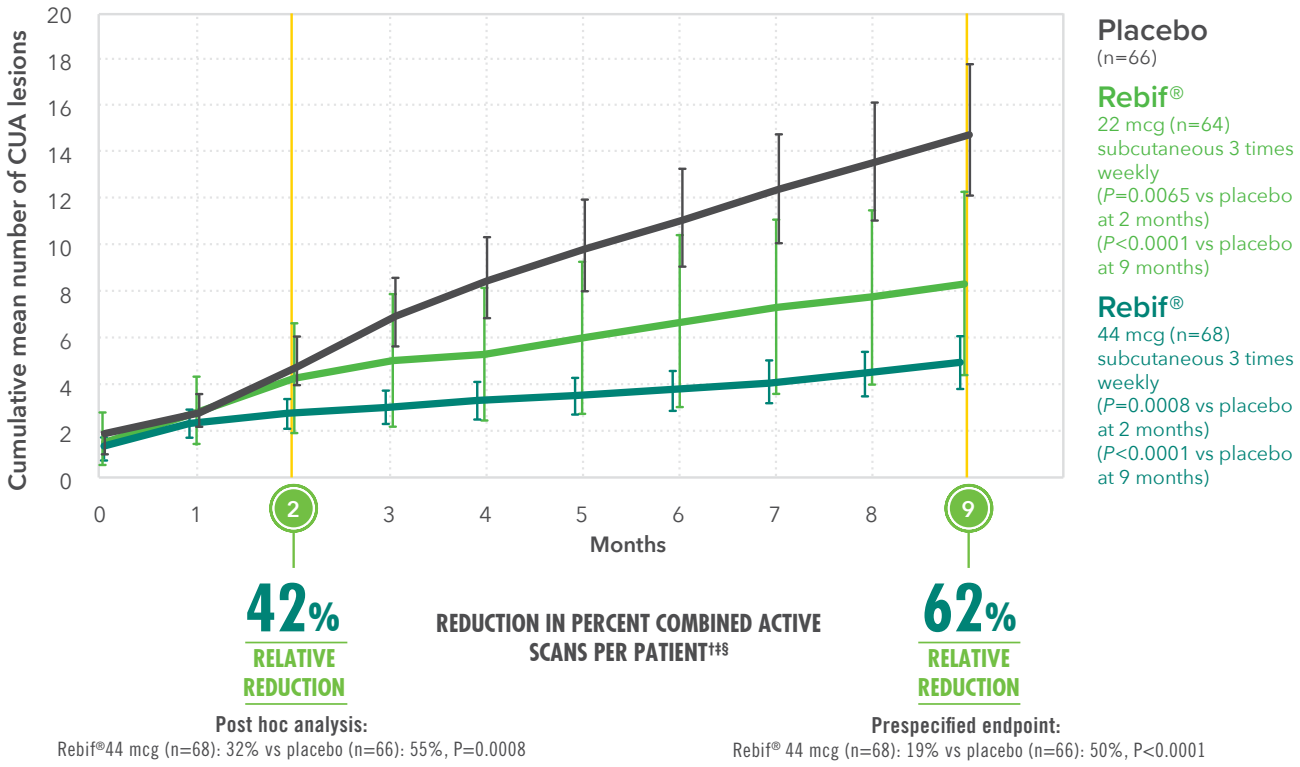
REBIF® DEMONSTRATED A SIGNIFICANT REDUCTION IN MRI LESIONS[4,6,9]

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=172) vs 2.25 for placebo (n=171); *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



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]

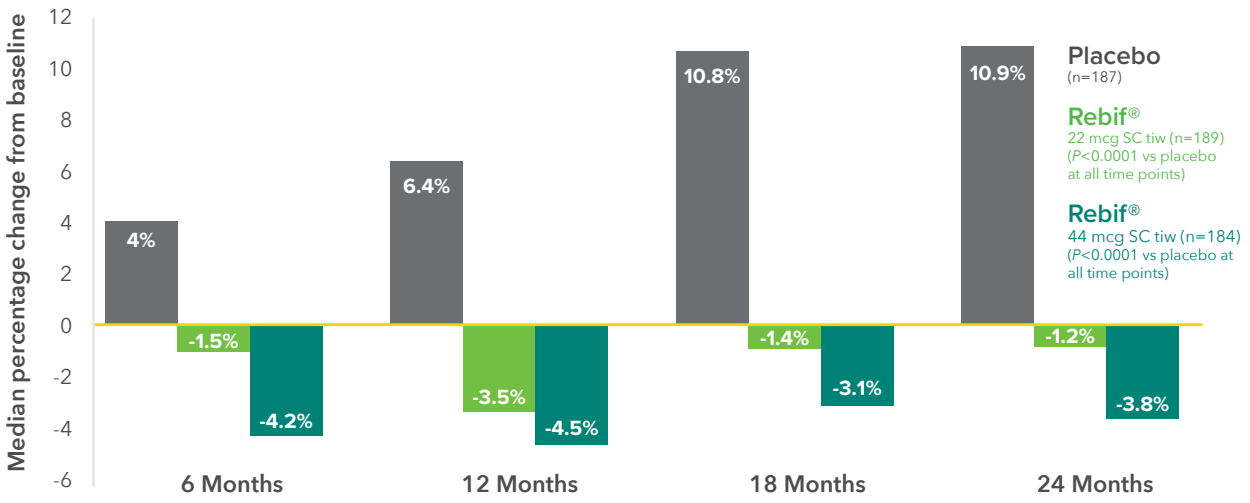
IMPORTANT SAFETY INFORMATION (cont'd)

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.

Please see additional Important Safety Information on page 9.

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

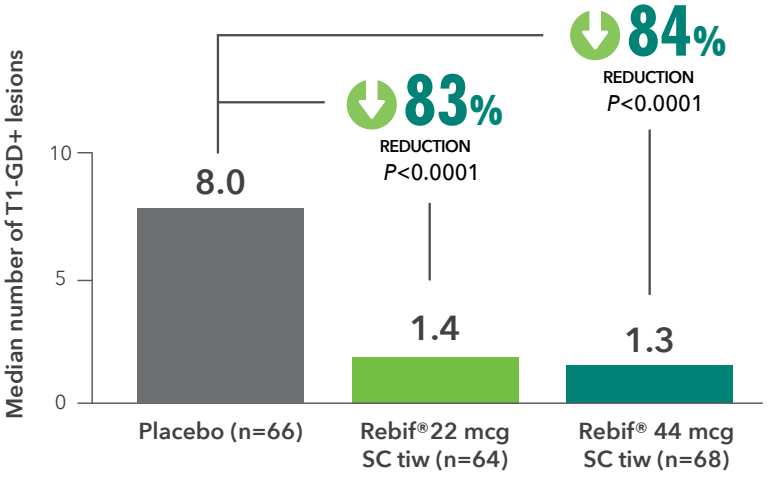
DECREASED PD/T2 LESION LOAD: BIANNUAL SCANS[9]



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)

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports.

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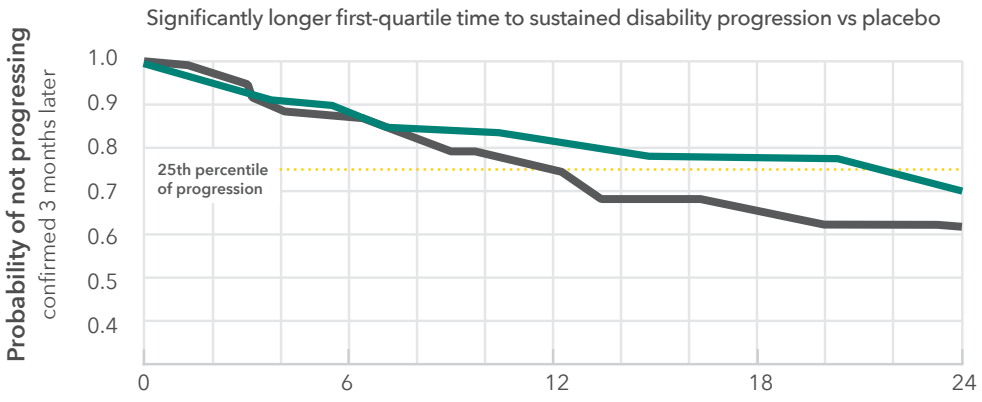
Please see additional Important Safety Information on page 9.

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)

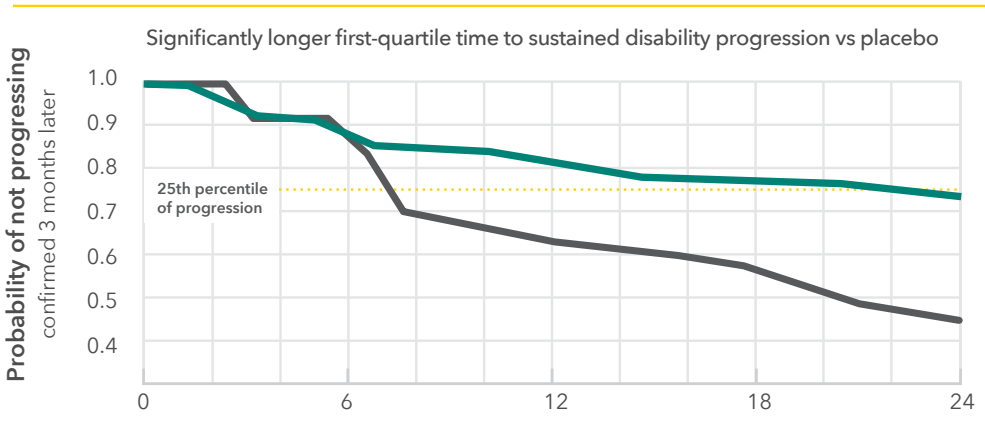


≈2× LONGER TO CDP*

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)

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

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.

Please see additional Important Safety Information on page 9.

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.
2. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. American Academy of Neurology. April 2018. Accessed June 16, 2020. https://aan.com/Guidelines/home/GuidelineDetail898.
3. Gajofatto A, Benedetti MD. Treatment strategies for multiple sclerosis: when to start, when to change, when to stop? World J Clin Cases. 2015;3(7):545-555.
4. Rebif® [Prescribing Information]. Rockland MA: EMD Serono, Inc.
5. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352(9139):1498-1504.
6. Data on file. EMD Serono, Inc. PRISMS study report.
7. Data on file. EMD Serono, Inc. PRISMS 2010 Confirming analysis.
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)

Data from a large human population-based cohort study, as well as other published studies over several decades, have not identified a drug-associated risk of major birth defects with 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 additional Important Safety Information on page 9.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

Rebif® is indicated 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.

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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.

Rebif® should be used with caution in patients with depression, a condition that is common 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®.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif®. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif® if hepatic injury occurs.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif®. 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. Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif® into affected area until fully healed; if multiple lesions occur, discontinue Rebif® until skin lesions are healed.

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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 a drug-associated risk of major birth defects with 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 the full Prescribing Information and Medication Guide located at the tabs above.

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