Rebif®
(interferon beta-1a)
subcutaneous injection

NOT ALL INTERFERONS ARE THE SAME

CONSIDER REBIF WHEN CHOOSING AN INTERFERON THERAPY

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.

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 inside and Rebif Full Prescribing Information.

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NOT ALL INTERFERONS ARE THE SAME

HIGH-DOSE, HIGH-FREQUENCY REBIF® WAS PROVEN SUPERIOR TO LOW-DOSE, LOW-FREQUENCY AVONEX® IN RELAPSE AND MRI CLINICAL MEASURES[1-5]

MORE PATIENTS

RELAPSE-FREE AT 24 WEEKS[1,2]

75%

vs 63% with Avonex

Rebif® 44 mcg: 75% (n=339) vs
Avonex 30 mcg: 63% (n=338), *P*<0.001

MORE PATIENTS

T2-ACTIVE LESION-FREE AT 64 WEEKS[1,2]

58%

vs 38% with Avonex

Rebif® 44 mcg: 58% (n=325) vs
Avonex 30 mcg: 38% (n=325), *P*<0.001

REBIF® IS THE ONLY PLATFORM INJECTABLE* WITH PROVEN SUPERIORITY AGAINST ANOTHER IFN IN A HEAD-TO-HEAD STUDY[2]

*Platform injectable refers to interferons and glatiramer acetate.

IMPORTANT SAFETY INFORMATION (cont'd)

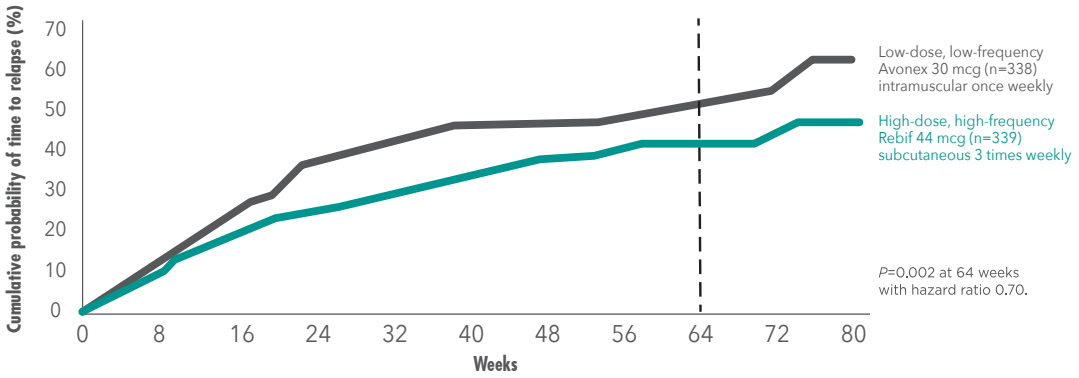
Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

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

Please see additional Important Safety Information on page 8.

REBIF® REDUCED THE RISK OF RELAPSE COMPARED WITH AVONEX[5]*

RISK OF RELAPSE OVER AN AVERAGE OF 64 WEEKS*



30%
REDUCTION
IN RISK OF RELAPSE

*The 40th-percentile time to first exacerbation was 13.5 months for Rebif®-treated patients and 6.7 months for Avonex-treated patients, demonstrating a delay in first exacerbation of approximately 6.8 months in favor of Rebif® for the 40th-percentile patients.

EVIDENCE STUDY DESIGN

EVidence of **I**nterferon **D**ose-response: **E**uropean **N**orth American **C**omparative **E**fficacy (**EVIDENCE**) was an assessor-blinded, parallel-group study conducted over an average of 64 weeks. Patients were randomized to receive Rebif® 44 mcg subcutaneously 3 times weekly (n=339) or Avonex 30 mcg intramuscularly once weekly (n=338). Outcomes measured included percentage relapse-free, MRI, safety, and antigenicity and were determined at 24, 48, and an average of 64 weeks.[2,3]

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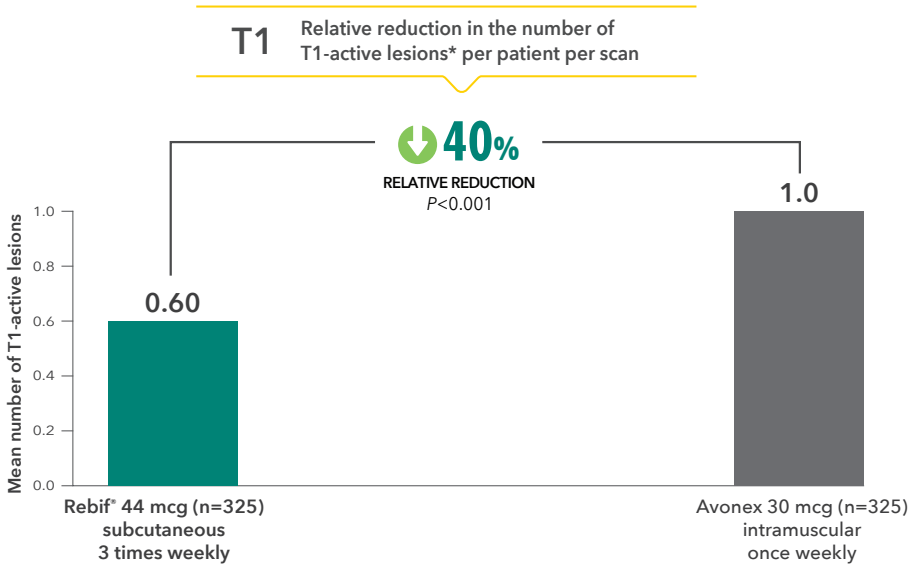
SIGNIFICANTLY FEWER T1-ACTIVE LESIONS vs AVONEX® AT 24 WEEKS[3,4]

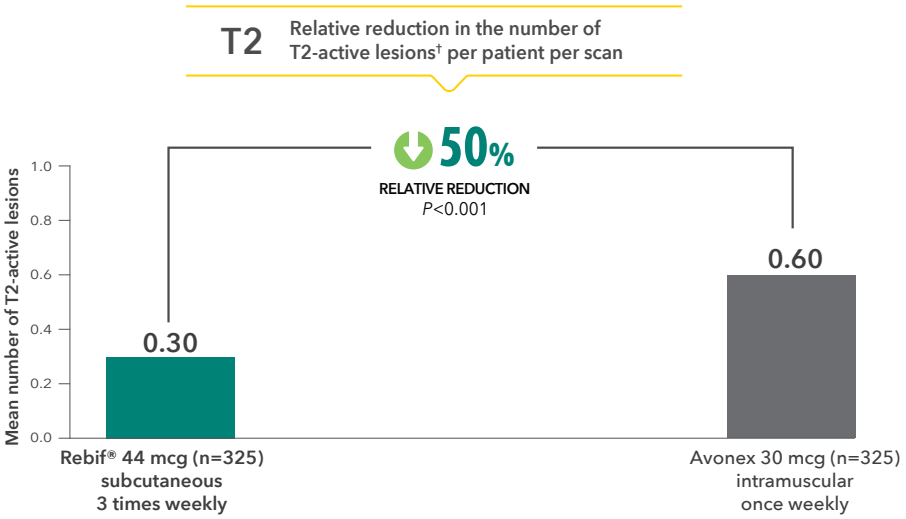
RELATIVE REDUCTION IN THE NUMBER OF T1-ACTIVE LESIONS* PER PATIENT PER SCAN



*New or enlarging lesions detected with Gd+-weighted MRI. The number of T1-active lesions per patient per scan at 24 weeks was a secondary MRI outcome measure in the EVIDENCE trial. The principal MRI outcome measure was the number of combined unique (CU) active lesions per patient per scan.

SIGNIFICANTLY FEWER T2-ACTIVE LESIONS vs AVONEX AT 24 WEEKS[4,6]

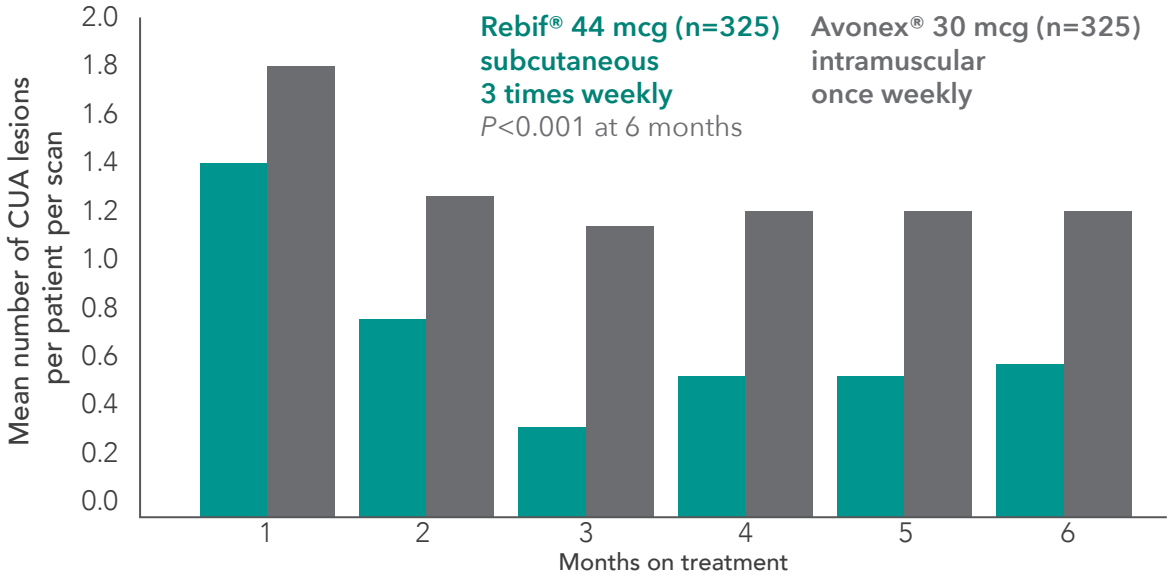
RELATIVE REDUCTION IN THE NUMBER OF T2-ACTIVE LESIONS† PER PATIENT PER SCAN



†New or enlarging lesions detected with PD/T2-weighted MRI. The number of T2-active lesions per patient per scan at 24 weeks was a MRI secondary outcome measure in the EVIDENCE trial.

LARGEST DIFFERENCE IN MRI ACTIVITY OBSERVED AT 2 TO 3 MONTHS OF STARTING REBIF®[3,4]

REDUCTIONS IN CUA LESIONS OVER 24 WEEKS



CUA: combined unique active.

IMPORTANT SAFETY INFORMATION (cont'd)

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. 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.

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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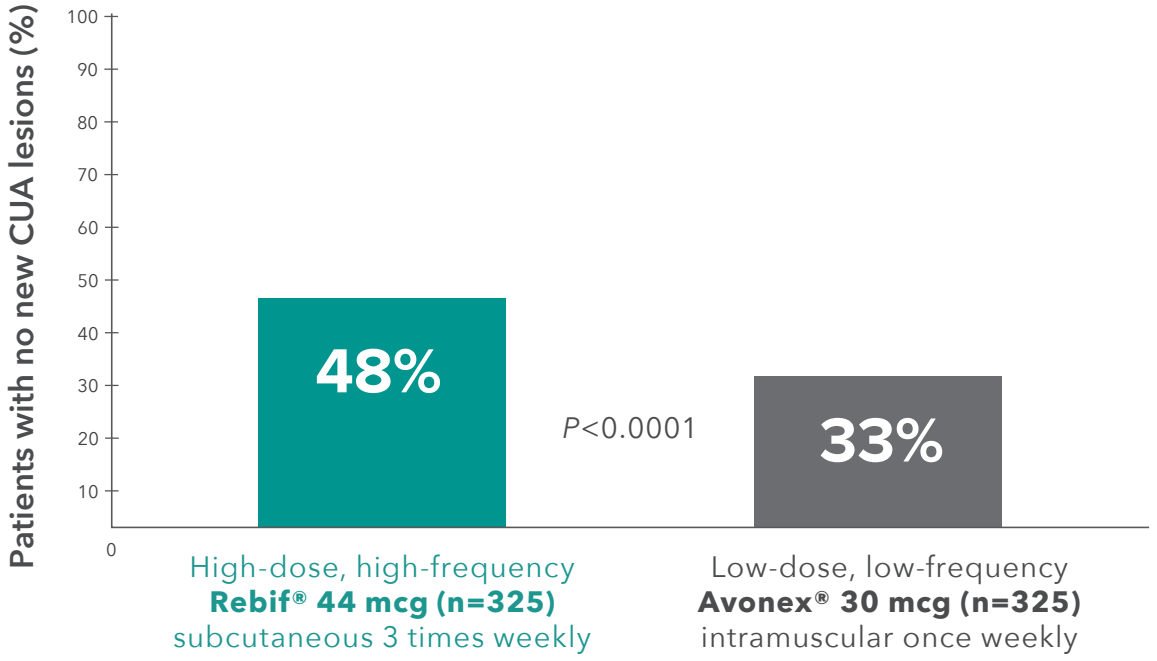
Please see additional Important Safety Information on page 8.

ALMOST HALF OF REBIF® PATIENTS EXPERIENCED NO NEW MRI ACTIVITY AT 24 WEEKS[4]

PERCENT OF PATIENTS WITH NO NEW CUA LESIONS AT 24 WEEKS



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.

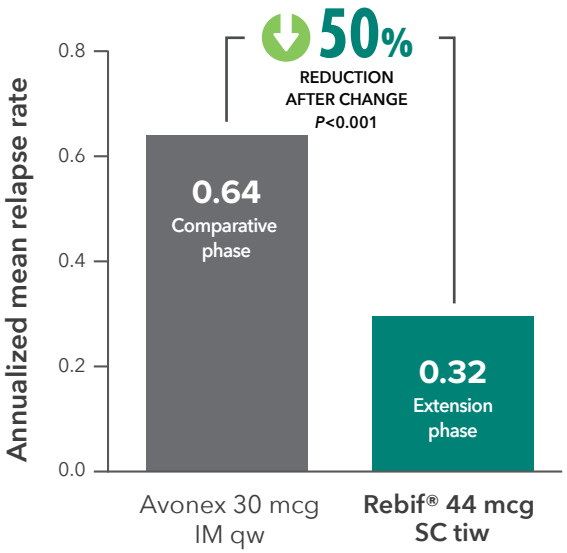
The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

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. 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.

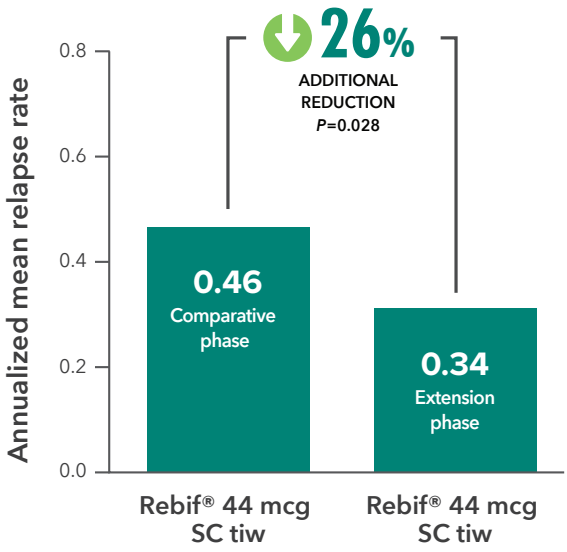
Please see additional Important Safety Information on page 8.

REBIF® PROVIDED ADDITIONAL RELAPSE REDUCTIONS IN THE EVIDENCE EXTENSION PHASE[7]

PATIENTS WHO TRANSITIONED FROM AVONEX® TO REBIF®



REBIF® PATIENTS WHO CONTINUED ON REBIF®



IM: intramuscular; qw: once weekly; SC: subcutaneous; tiw: 3 times weekly.

- Patients who had been on Avonex for 6 months and transitioned to Rebif® had a 50% reduction in relapse rate at an average of 8 months post-transition (n=223)
- Patients who elected to stay on Rebif® saw an additional 26% reduction in relapse rate (n=272)
- Compared with Avonex, adverse events were similar over an average of 64 weeks, despite higher, more frequent dosing with Rebif®. Injection-site disorders (85% vs 33%), hepatic function disorders (18% vs 10%), and white blood cell disorders (14% vs 5%) were more frequent with Rebif®. Flu-like symptoms were more frequent with Avonex (53% vs 45%)

The extension phase of the EVIDENCE study was an open-label, within-treatment-group comparison of patients who elected to remain in the study and take Rebif® 44 mcg subcutaneously 3 times weekly (n=272) for an average of 8 months vs their final 6 months on Avonex intramuscularly (n=223). The primary endpoint of the study was the percent of relapse-free patients. Other outcome measures included MRI, safety, and antigenicity.

Of the 605 patients receiving therapy at the end of the comparative phase of EVIDENCE, 495 patients enrolled in the extension phase of the study. In the extension phase, all patients were offered the option of either taking Rebif® 44 mcg 3 times weekly or leaving the study. Clinical assessments were not blinded, but MRI evaluations were blinded. All assessments were within-treatment-group comparisons. Patients were followed for an average of 8 months post-transition. Annualized relapse rate is based on a time-adjusted analysis.

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Please see additional Important Safety Information on page 8.

REFERENCES

1. Rebif® [Prescribing Information]. Rockland, MA: EMD Serono, Inc.
2. Panitch H, Goodin D, Francis G, et al; for EVIDENCE (EVidence of Interferon Dose-response-European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci*. 2005;239(1):67-74.
3. Data on file. EMD Serono, Inc. EVIDENCE study report 2001.
4. Panitch H, Goodin DS, Francis G, et al; EVIDENCE Study Group and the University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. *Neurology*. 2002;59(10):1496-1506.
5. Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response–European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. *Clin Ther*. 2007;29(9):2031-2048.
6. Data on file. EMD Serono, Inc. EVIDENCE ICS 2003.
7. Schwid SR, Thorpe J, Sharief M, et al; EVIDENCE (EVidence of Interferon Dose-Response: European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: the EVIDENCE Study. *Arch Neurol*. 2005;62(5):785-792.

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INDICATION AND IMPORTANT SAFETY INFORMATION

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Please see the full Prescribing Information and Medication Guide located at the tabs above.

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