



CONSIDER REBIF

FOR YOUR RELAPSING MS PATIENTS THINKING ABOUT FAMILY PLANNING

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.

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 inside and linked Rebif full Prescribing Information

A PATIENT'S PERSONAL PRIORITIES MAY NEED TO BE FACTORED INTO THEIR RMS TREATMENT PLAN

FAMILY PLANNING MAY RAISE TREATMENT-RELATED QUESTIONS FROM YOUR PATIENTS^{1,3}

Should I stay on treatment while trying to get pregnant?

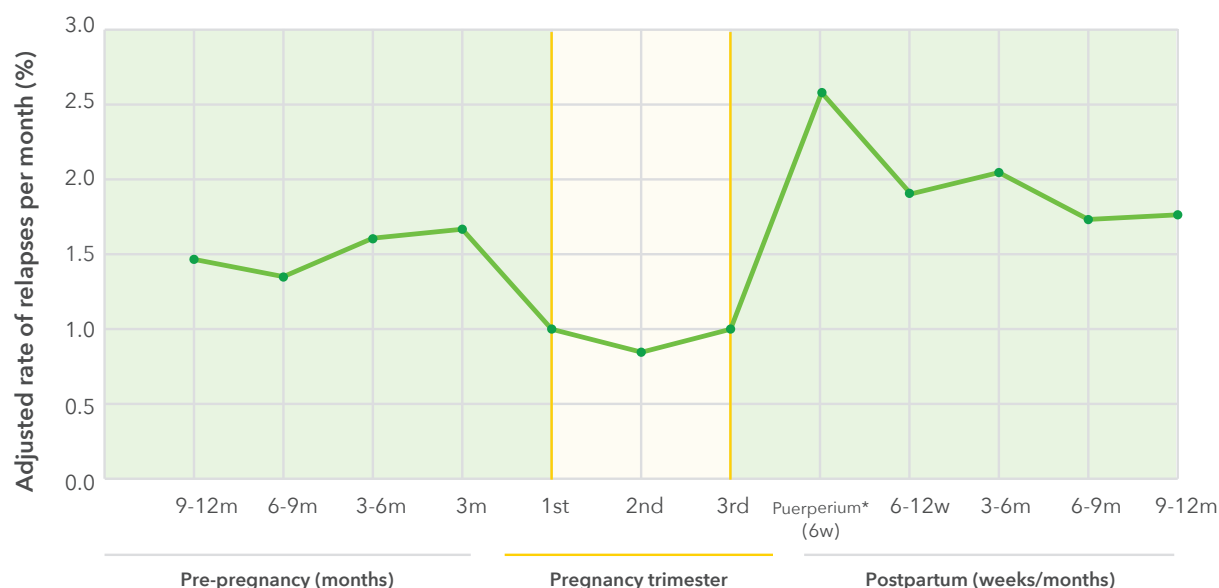


How can I protect myself against relapses after my baby is born?

THE RISK OF RELAPSE DIFFERS IN PRE-PREGNANCY, PREGNANCY, AND POSTPARTUM PHASES³

In a retrospective study, the rate of relapse in women with MS was evaluated before, during, and after pregnancy.

ADJUSTED MONTHLY RATES OF TOTAL RELAPSES FOR PATIENTS WITH MS³



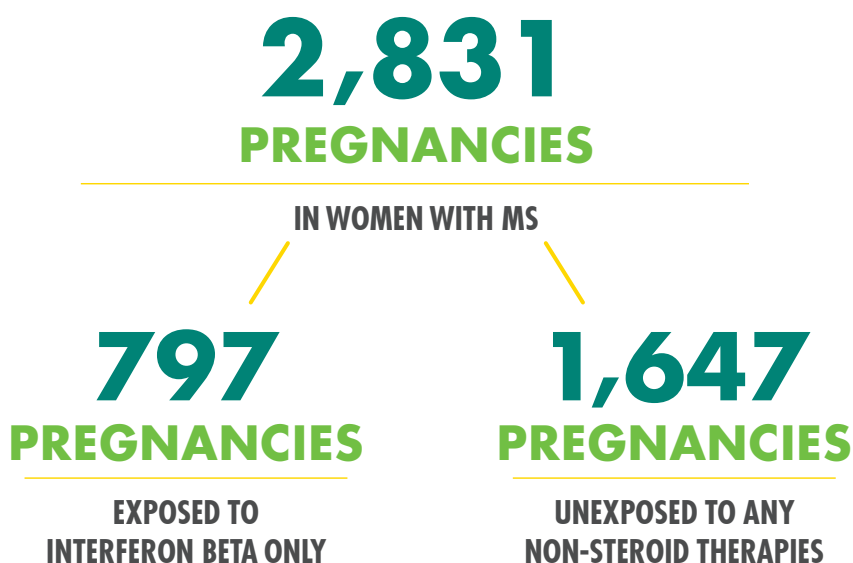
This was a retrospective administrative-claims database study using the IQVIA Real-World Data Adjudicated Claims-US database between January 1, 2006, and June 30, 2015 (n=2,158).

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.

THE REBIF® PI NOW INCLUDES UPDATES BASED ON THE FOLLOWING HUMAN DATA¹

THESE DATA ARE FROM A LARGE, REGISTER-BASED STUDY (NORDIC REGISTRY)



Another register-based study (European registry) of women with MS exposed to interferon beta during pregnancy did not identify an association between the use of interferon beta products during early pregnancy and an increased risk of major birth defects.*

*There is no internal comparator group to contextualize the rates observed within this study.



PREGNANCY AND LACTATION LABELING RULE (PLLR): The PLLR requires changes to the content and reformatting of information presented in prescription drug labeling. The PLLR removes pregnancy letter categories (A, B, C, D, and X). The PLLR requires a label update to reflect the risks of a product to pregnancy. To provide more meaningful information for clinicians, these updates are designed to assist healthcare providers in assessing benefit versus risk and in subsequent counseling of pregnant and nursing women.

Key Rebif® PI updates include:

- Removal of category C designation
- Inclusion of a large, register-based study, as well as other previously published studies
- Inclusion of human data regarding lactation, birth defects, and miscarriage

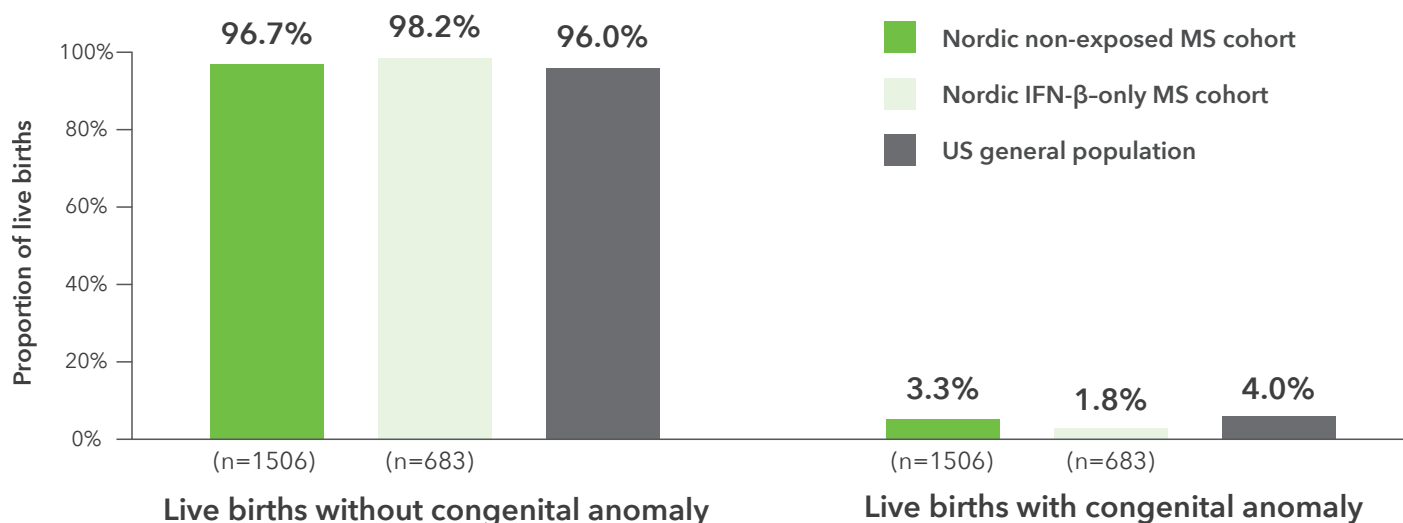
IMPORTANT SAFETY INFORMATION (cont'd)

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

Rebif®
(interferon beta-1a)
subcutaneous injection

NO IDENTIFIED DRUG-ASSOCIATED RISK OF MAJOR BIRTH DEFECTS WITH THE USE OF INTERFERON BETA PRODUCTS DURING EARLY PREGNANCY^{1,4}

PREGNANCY OUTCOMES DATA FOR LIVE BIRTHS FROM THE NORDIC MS PREGNANCY REGISTRY AND US GENERAL POPULATION*



*The data shown above are from an analysis reported in the Hellwig and Burkill publications, which is a different analysis than reported in the Prescribing Information.

Outcomes regarding the risk of low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent¹

- Two small cohort studies suggested a decrease in mean birth weight. This finding was not confirmed in larger observational studies
- Two small cohort studies observed an increased prevalence of miscarriage, which was only statistically significant in one study. Most studies enrolled patients in later pregnancy, which made it difficult to ascertain the true percentage of miscarriages
- One small cohort study observed a significantly increased risk of pre-term birth

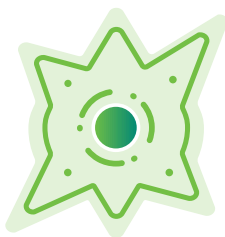
In an animal study, no adverse effects on embryofetal development were observed; however, the possibility of adverse effects cannot be ruled out because of the small number of animals tested (6 per dose group at each developmental period).

IMPORTANT SAFETY INFORMATION (cont'd)

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.

TRANSFER OF IFN- β INTO BREAST MILK

Limited published literature has described the presence of interferon beta-1a products in human milk at low levels. There is no data on the effects of interferon beta-1a on milk production.¹



Interferons (IFNs) are large (22,500 Da) polar molecules that are highly bound to lymphocytes and other immune cells suggesting that they do not readily pass into breast milk^{5,6}



IFNs exhibit poor oral absorption⁷

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rebif® and any potential adverse effects on the breastfed child from Rebif® or from the underlying maternal condition.¹

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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REFERENCES

1. Rebif® [Prescribing Information]. Rockland, MA: EMD Serono, Inc.
2. 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- β 1a in relapsing-remitting multiple sclerosis. *Ann Neurol*. 1999;46(2):197-206.
3. Houtchens MK, Edwards NC, Phillips AL. Relapses and disease-modifying drug treatment in pregnancy and live birth in US women with MS. *Neurology*. 2018;91(17):e1570-e1578.
4. Hellwig K, et al. ECTRIMS 2018.
5. Hale TW, Siddiqui AA, Baker TE. Transfer of interferon β -1a into human breastmilk. *Breastfeed Med*. 2012;7(2):123-125.
6. Almas S, Vance J, Baker T, Hale T. Management of multiple sclerosis in the breastfeeding mother. *Mult Scler Int*. 2016;2016:6527458.
7. Drugs and Lactation Database (LactMed). Interferon beta. National Library of Medicine; 2006. Updated June 15, 2020. Accessed October 29, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK501922/>.

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.

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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