Rebif®
(interferon beta-1a)
subcutaneous injection

CONSIDER REBIF

FOR YOUR RELAPSING MS PATIENTS THINKING ABOUT FAMILY PLANNING

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.

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.

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. 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.

Please see Important Safety Information throughout and on page 7, as well as Rebif Prescribing Information and Medication Guide.

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[1,2]

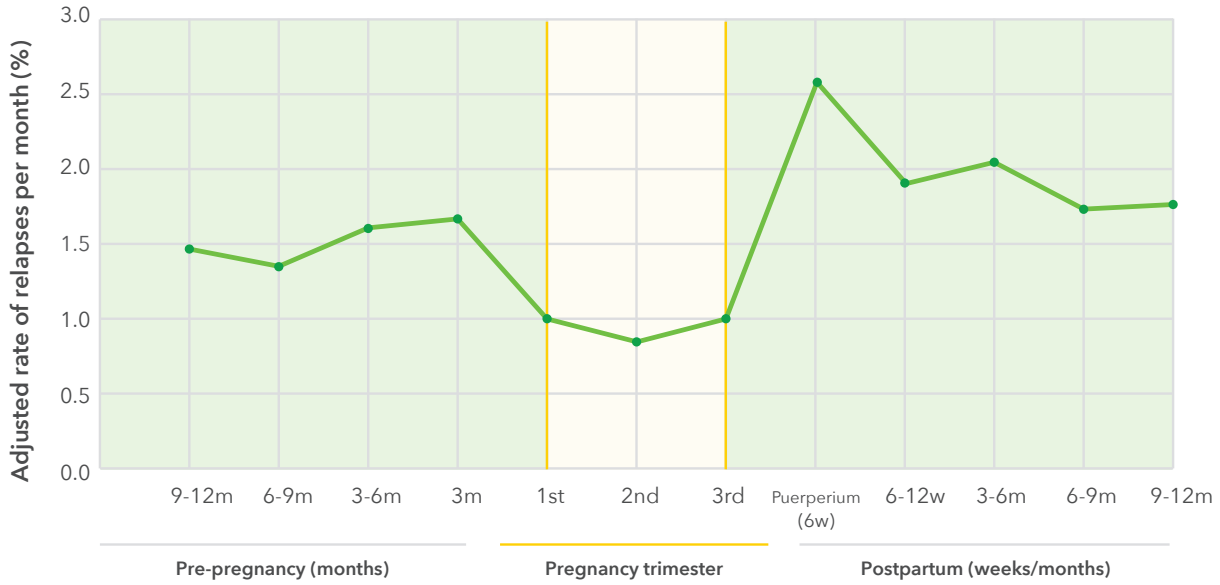
Should I stay on treatment while trying to get pregnant?

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

THE RISK OF RELAPSE DIFFERS IN PRE-PREGNANCY, PREGNANCY, AND POSTPARTUM PHASES[2]

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 MS[2]



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)

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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THE REBIF® PI NOW INCLUDES UPDATES BASED ON THE FOLLOWING HUMAN DATA[1]

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

2,831
PREGNANCIES
IN WOMEN WITH MS

797
PREGNANCIES
EXPOSED TO INTERFERON BETA ONLY

1,647
PREGNANCIES
UNEXPOSED TO ANY NON-STEROID THERAPIES

Tell your patients to stop taking Rebif immediately if they become pregnant and reach out to you for more information.

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)

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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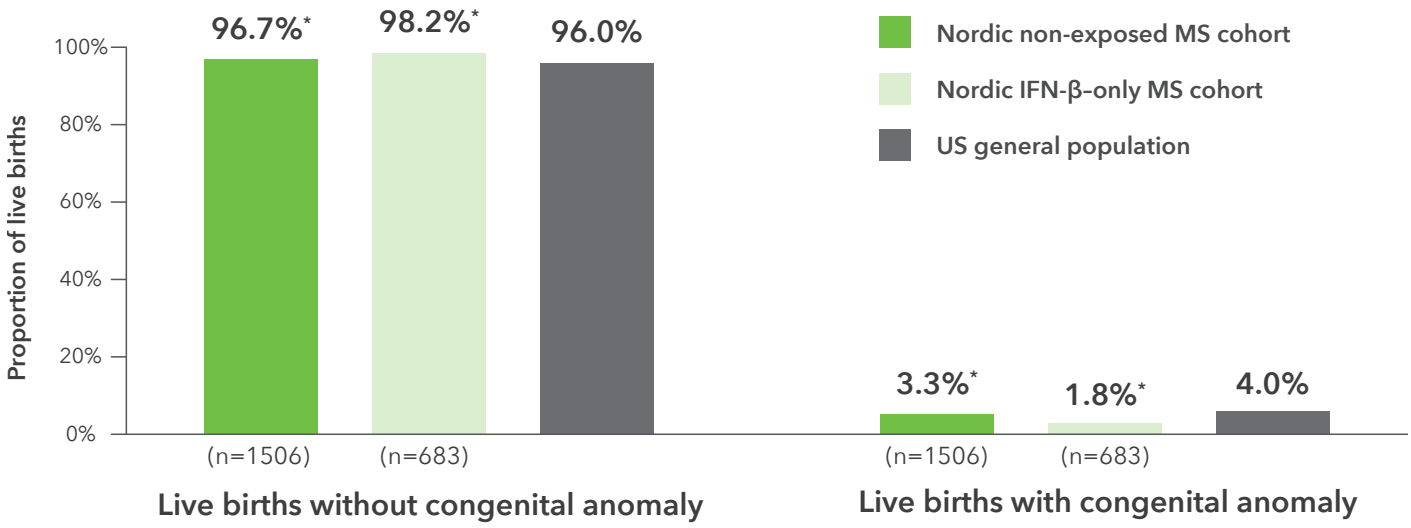
NO IDENTIFIED INCREASED DRUG-ASSOCIATED RISK OF MAJOR BIRTH DEFECTS WITH THE USE OF INTERFERON BETA PRODUCTS DURING EARLY PREGNANCY[1,3]

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



*The data shown are from an analysis reported in the Hellwig publication, 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 inconsistent[1]

- 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)

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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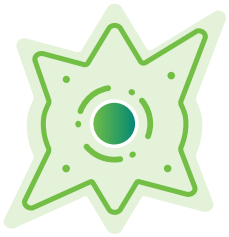
TRANSFER OF IFN-β INTO BREAST MILK

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[4,5]

IFNs exhibit poor oral absorption[6]

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)

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. Rebif® [Prescribing Information]. Rockland, MA: EMD Serono, Inc.
2. 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.
3. Hellwig K, et al. ECTRIMS 2018.
4. Hale TW, Siddiqui AA, Baker TE. Transfer of interferon β-1a into human breastmilk. *Breastfeed Med*. 2012;7(2):123-125.
5. Almas S, Vance J, Baker T, Hale T. Management of multiple sclerosis in the breastfeeding mother. *Mult Scler Int*. 2016;2016:6527458.
6. 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)

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.

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