"I WANT TO START PLANNING A FAMILY. SHOULD I RETHINK MY MS TREATMENT PLAN?"

CLICK HERE FOR MORE INFO ABOUT PRESCRIBING REBIF®

PREGNANCY CAN AFFECT THE RISK OF MS RELAPSE[1]

For MS patients considering becoming pregnant, choosing a treatment plan is a critical decision. The risk of relapse differs before, during, and after pregnancy.

Consider Rebif® for patients who wish to continue treating their MS while trying to get pregnant. There are no contraception requirements for Rebif®.[2]

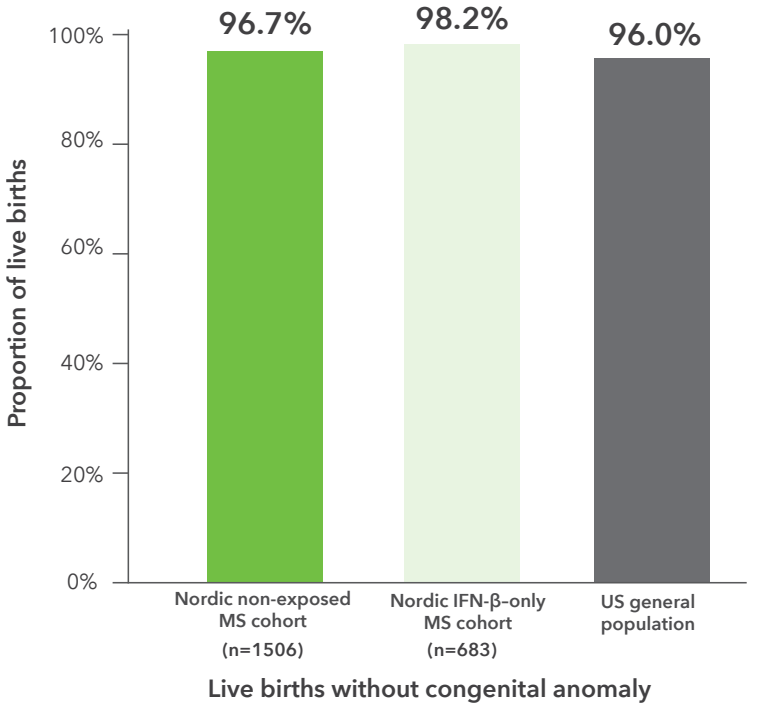
THERE WAS NO IDENTIFIED RISK OF MAJOR BIRTH DEFECTS WITH INTERFERON BETA DURING EARLY PREGNANCY[2,3]*

A large, register-based study (Nordic Registry) of 2,831 pregnancies in women with MS (797 were exposed to interferon beta and 1,647 were unexposed to any non-steroid therapy for MS) did not identify drug-associated risk of major birth defects with the use of interferon beta products during early pregnancy.[2]

*See page 2 for more information ›

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

PREGNANCY OUTCOMES DATA FOR LIVE BIRTHS FROM THE NORDIC MS PREGNANCY REGISTRY AND US GENERAL POPULATION[2,3†]



INDICATION

Rebif® (interferon beta-1a) 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.

Please see additional Important Safety Information on page 4 and the Full Prescribing Information and Medication Guide.

Rebif® (interferon beta-1a) subcutaneous injection

ADDITIONAL PREGNANCY STUDY INFORMATION

Outcomes regarding the risk of low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent[2]

- 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 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 embryo fetal 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).

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)

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®.

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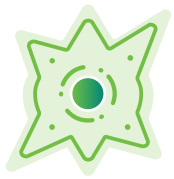
Rebif® (interferon beta-1a) subcutaneous injection

TREATMENT AFTER PREGNANCY

As you consider starting or restarting treatment after a patient's pregnancy, keep in mind the potential increased risk of relapses in the postpartum phase.[1]

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.[2]



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]

Interferons 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.[2]

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.

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Rebif® (interferon beta-1a) subcutaneous injection

INDICATION AND IMPORTANT SAFETY INFORMATION

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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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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.

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.

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.

REFERENCES

1. 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. **2.** Rebif® [Prescribing Information]. Rockland, MA: EMD Serono, Inc. **3.** Hellwig K, Geissbuehler Y, Sabidó M, 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/

Please see Full Prescribing Information and Medication Guide.