Rebif® (interferon beta-1a) subcutaneous injection

WHAT DO YOU CONSIDER WHEN YOUR RMS PATIENTS ARE THINKING ABOUT FAMILY PLANNING?

Learn how the Rebif® label has changed

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.

Please see Important Safety Information throughout and on page 8, as well as Rebif Prescribing Information and Medication Guide.

The Rebif® label now includes updated pregnancy outcomes and lactation information[1]

KEY 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

PREGNANCY AND LACTATION LABELING RULE (PLLR): Since June 30, 2015, the FDA has been making revisions to the labels of all prescription drugs to remove the pregnancy letter categorization, with the process to be completed by June 2020. The Pregnancy and Lactation Labeling Rule (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. These updates are designed to assist healthcare providers in assessing benefit versus risk and in subsequent counseling of pregnant and nursing women.

Updates based on inclusion of the following human data[1]

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

2,831
WOMEN
WITH MS INCLUDED IN THESE STUDIES

797
WOMEN
EXPOSED TO INTERFERON BETA DURING PREGNANCY

1,647
WOMEN
UNEXPOSED TO ANY NON-STEROID THERAPIES DURING PREGNANCY

NO INCREASED DRUG-ASSOCIATED RISK OF MAJOR BIRTH DEFECTS WITH INTERFERON BETA USE DURING EARLY PREGNANCY

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.

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The Pregnancy and Lactation Labeling Rule (PLLR) resulted in removal of Pregnancy Category C.

Now includes a large, register-based study, as well as other previously published studies. This section no longer states there are no adequate and well-controlled studies in pregnant women.

Epidemiological data from several sources do not suggest a clear relationship between interferon beta usage and major birth defects during early pregnancy.

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

It is unclear if doses of interferon beta greater than those used clinically results in an increased rate of abortion in pregnant animals.

Label now includes U.S. general population data on estimated risk of major birth defects (2%-4%) and miscarriage (15%-20%).

However, the risk of major birth defects and miscarriage for the indicated population is unknown.

IMPORTANT SAFETY INFORMATION (cont'd)

Anaphylaxis and other allergic reactions (some severe) have been reported. Discontinue Rebif if anaphylaxis occurs.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Pregnancy: 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 data.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from a large 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 the use of 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 *(see Data)*.

It is unclear whether, as a class of products, administration of interferon beta therapies to pregnant animals at doses greater than those used clinically results in an increased rate of abortion. The potential for REBIF to have adverse effects on embryofetal development has not been fully assessed in animals [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Majority of observational studies in humans did not find an association between interferon beta usage and major birth defects during early pregnancy.

Label now includes information from **2,831** pregnancy outcomes from women with MS in Finland and Sweden.

797 women with MS were exposed to interferon beta during early pregnancy, with no evidence of increased risk of major birth defects, when compared to **1,647** women with MS unexposed to any non-steroid therapy.

Care must be used when interpreting this information because there were limitations in obtaining complete data; however, no increased risks were observed for miscarriages or ectopic pregnancies.

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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Data

Human data

The majority of observational studies reporting on pregnancies exposed to interferon beta products did not identify an association between the use of interferon beta products during early pregnancy and an increased risk of major birth defects.

In a population-based cohort study conducted in Finland and Sweden, data were collected from 1996—2014 in Finland and from 2005—2014 in Sweden on 2,831 pregnancy outcomes from women with MS. 797 pregnancies were in women exposed to interferon beta only. No evidence was found of an increased risk of major birth defects among women with MS exposed to interferon beta products compared to women with MS that were unexposed to any non-steroid therapy for MS (n=1,647) within the study. No increased risks were observed for miscarriages and ectopic pregnancies, though there were limitations in obtaining complete data capture for these outcomes, making the interpretation of the findings more difficult.

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Small cohort studies provide the following information when examining pregnancies exposed to interferon beta products.

- Two small studies found a decrease in mean birth weight, but this finding was not confirmed in larger observational studies
- Two small studies found an increased prevalence of miscarriage, but the finding was only statistically significant in one study, and most patients were in later pregnancy
- One small study found an increased risk of preterm birth

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Data

Human data

Two small cohort studies that examined pregnancies exposed to interferon beta products (without differentiating between subtypes of interferon beta products) suggested that a decrease in mean birth weight may be associated with interferon beta exposure during pregnancy, but this finding was not confirmed in larger observational studies. Two small studies observed an increased prevalence of miscarriage, although the finding was only statistically significant in one study. Most studies enrolled patients later in pregnancy, which made it difficult to ascertain the true percentage of miscarriages. In one small cohort study, a significantly increased risk of preterm birth following interferon beta exposure during pregnancy was observed.

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.

No update since previous label.

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.

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.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Data

Animal data

In a study in pregnant cynomolgus monkeys, interferon beta was administered daily (intramuscular doses approximately 1, 2, and 7 times the maximum recommended cumulative weekly human dose, based on body surface area) either throughout the period of organogenesis or later in pregnancy (gestation day 90 to term). 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 (six per dose group at each developmental period).

Limited data are available that describe low levels of interferon beta products in human milk.

With this new information, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rebif, as well as any potential adverse effects on the breastfed child from Rebif.

The Medication Guide was updated regarding breastfeeding. It now states:

Rebif may pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you take Rebif.

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.

8 USE IN SPECIFIC POPULATIONS

8.2 Lactation

Risk Summary

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

Indication and Important Safety Information

INDICATION

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Rebif®
(interferon beta-1a)
subcutaneous injection

20+ years of combined clinical trial and real-world experience, resulting in a well-established safety profile[1,2]

150 THOUSAND+
US patients treated since approval[2]

NO PML
Has been associated with Rebif[1]

20+ YEAR
Well-established safety profile[1]

SELECTED IMPORTANT SAFETY INFORMATION:

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1. Rebif [Prescribing Information]. Rockland, MA: EMD Serono, Inc. **2.** Data on file. EMD Serono, Inc. NS/RS patients through LifeLines.

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