This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Report on Investigation Results

March 2, 2022
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Interferon beta-1a (genetical recombination) b. Interferon beta-1b (genetical recombination)
[Brand name]	a. Avonex IM Injection PEN 30 μg, Avonex IM Injection Syringe 30 μg b. Betaferon for SC injection 960 IU
[Approval holder]	a. Biogen Japan Ltd. b. Bayer Yakuhin, Ltd.
[Indications]	a. Prevention of relapse in multiple sclerosis b. Prevention of relapse and delaying the progression in multiple sclerosis
[Dosage and administration]	a. The usual adult dose is 30 μg of interferon beta-1a (genetical recombination) intramuscularly administered once weekly. b. The usual adult dose is 800 IU subcutaneously administered on alternate days.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Interferon beta-1a (genetical recombination, hereinafter referred to as “IFNβ-1a”) was approved in the US in May 1996 and has since been approved in a total of 85 countries and regions including the EU. Interferon beta-1b (genetical recombination, hereinafter referred to as “IFNβ-1b”) was approved in the US in July 1993 and has since been approved in a total of 92 countries and regions including the EU.

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In Japan, IFNβ-1a was approved in July 2006 for the indication of “prevention of relapse in multiple sclerosis,” and IFNβ-1b was approved in September 2000 for the indication of “prevention of relapse and delaying the progression in multiple sclerosis.”

Pregnant women or women who may be pregnant have been specified in the CONTRAINDICATIONS section of the electronic package inserts of IFNβ-1a and IFNβ-1b (hereinafter referred to as “IFNβ”) since the time of approval of the drug.

In the EU, at the time of initial approval of the drug (March 1997 for IFNβ-1a, November 1995 for IFNβ-1b), administration to pregnant women or women who may be pregnant was contraindicated. From 2009 to 2017, based on the registry studies in pregnant women exposed to IFNβ conducted in 26 countries in Europe, and Scandinavian countries (Finland and Sweden), respectively, (hereinafter referred to as the “European registry study” and the “Scandinavian registry study,” respectively) (see 3.1 and 3.2), contraindication for administration to pregnant women or women who may be pregnant was lifted in 2019 in the EU. Meanwhile in the US, the CONTRAINDICATIONS section of the package inserts has not specified pregnant women or women who may be pregnant since the initial approval (May 1996 for IFNβ-1a, July 1993 for IFNβ-1b).

Recently in Japan, the marketing authorization holder (hereinafter referred to as the MAH) of IFNβ-1a has requested a consultation for removal of the language concerning pregnant women or women who may be pregnant in the CONTRAINDICATIONS section of the package insert of IFNβ-1a, to be replaced with precaution that the drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks, with the results of the registry studies with IFNβ-1a or IFNβ-1b (see 3.1 to 3.3) as the major basis. The MAH of IFNβ-1b meanwhile, requested a consultation with the intention to outline in the package insert such overseas registry studies as well as the post-marketing use-result surveys. In response to these requests, the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) has decided to conduct this investigation.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Outline of Investigation by PMDA

1. Up to the marketing approval in Japan

When IFNβ-1b was approved for marketing in Japan, administration of IFNβ-1b to pregnant women or women who may be pregnant was contraindicated and the reason of the contraindication was stated in the Pregnant Women section that "foetal deaths and spontaneous abortions have been reported as observed in an animal study (monkeys) at higher doses of this drug." (Betaferon for SC injection 960 IU, e-package insert)

Similarly, administration of IFNβ-1a to pregnant women or women who may be pregnant were contraindicated in the package insert of the drug and the reason for the contraindication was stated in the Pregnant Women section that "spontaneous abortions have been reported as observed in an animal study (monkeys) at higher doses of this drug." (Avonex IM Injection PEN 30 μg, Avonex IM Injection Syringe 30 μg, electronic package insert)

2. Current description of overseas package inserts

The current description related to administration to pregnant women or women who may be pregnant in the US, EU (UK included), German, French, Canadian, and Australian package inserts of IFNβ-1a and IFNβ-1b was as follows (Appendix 1, Appendix2):

2.1 The US package insert

2.1.1 IFNβ-1a

The CONTRAINDICATIONS section has not specified pregnant women or women who may be pregnant since the time of approval. The description in the Pregnancy section is as follows:

- The majority of observational studies reporting on pregnancies exposed to Interferon beta[1] products did not identify an association between the use of Interferon beta products during early pregnancy and an increased risk of major birth defects.
- The results of the Scandinavian registry study (see 3.2) on women with multiple sclerosis (hereinafter referred to as "MS") found no evidence of an increased risk of major birth defects, miscarriages and ectopic pregnancies among women with MS exposed to Interferon beta compared to women with MS that were unexposed to IFNβ or any non-steroid therapy for MS.

[1] For section 2 to 4, "interferon beta" and "interferon β" in the cited document are referred to as "Interferon beta" in this report.

- 2 small cohort studies[2] that examined pregnant women exposed to Interferon beta 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[2]. Among the 2 small cohort studies, only 1 study[2] observed a statistically significant increase of miscarriage.
- In pregnant monkeys given Interferon beta at 100 times the recommended weekly human dose (based upon a body surface area [mg/m^2] comparison), no adverse effects on embryofetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level[2].
- No abortifacient effects were observed[2] in monkeys treated at 2 times the recommended weekly human dose (based upon mg/m^2).

2.1.2 IFNβ-1b

The CONTRAINDICATIONS section has not specified pregnant women or women who may be pregnant since the time of approval. The description in the Pregnancy section is as follows:

- Although there have been no well-controlled studies in pregnant women, available data have not generally indicated a drug-associated risk of major birth defects with IFNβ-1b during pregnancy.
- When IFNβ-1b was administered to pregnant rhesus monkeys throughout the period of organogenesis, a dose-related abortifacient effect was observed[2].

2.2 The EU (UK included) package insert

The Contraindications section at the time of initial approval specified initiation of treatment during pregnancy and the Pregnancy section noted an increased risk of spontaneous abortion. Subsequently, with the European and Scandinavian registry studies conducted (see 3.1 and 3.2), the language concerning pregnant women or women who may be pregnant was deleted from the Contraindications section in September 2019 and the following statements were included in the Pregnancy section of the package insert of IFNβ.

- A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to Interferon beta or such exposure during the first trimester of

[2] No reference is made.

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pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when Interferon beta use was contraindicated during pregnancy, and treatment was likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

- Based on animal data, there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to Interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.
- If clinically needed, the use of IFNβ-1a or IFNβ-1b may be considered during pregnancy.

2.3 German package insert

Pregnant women or women who may be pregnant are not specified in the Contraindications (Gegenanzeigen) section in either of the package insert of IFNβ-1a or -1b. The Pregnancy (Schwangerschaft) section contains similar statements to the EU Package inserts.

2.4 French package insert

Pregnant women or women who may be pregnant are not specified in the Contraindications (Contre-indications) section in either of the package insert of IFNβ-1a or -1b. The Pregnancy (Grossesse) section contains similar statements to the EU Package inserts.

2.5 Canadian package insert

2.5.1 IFNβ-1a

Pregnant women or women who may be pregnant are not specified in the CONTRAINDICATIONS section. The Pregnant Women section notes as follows:

- There are no adequate and well-controlled studies in pregnant women. The administration during confirmed pregnancy should be avoided, unless clearly needed.
- In a European registry study (see 3.1), the rates of adverse pregnancy outcomes were in line with reference ranges published in the literature.
- Data from a pregnancy registry study that included 302 MS patients exposed to IFNβ-1a in the United States (hereinafter referred to as the “US registry study”) (see 3.3) found an increased incidence of major birth defects compared to the reference population.

Data from the Scandinavian registry study (see 3.2) have not indicated an increased risk of major congenital anomalies after exposure to Interferon beta. Given these contrasting data, it is unclear whether IFNβ-1a has teratogenic effects.

- In each of the studies discussed above, the duration of exposure during the first trimester was uncertain since data were collected when Interferon beta use was contraindicated or strongly advised against during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health.
- In pregnant monkeys given IFNβ-1a at 100 times the recommended weekly human dose (based upon mg/m^2), no teratogenic effects on fetal development were observed.
- The risk of spontaneous abortions in pregnant women exposed to Interferon beta cannot be evaluated based on the currently available data.

2.5.2 IFNβ-1b

Pregnant women or women who may be pregnant are not specified in the CONTRAINDICATIONS section. The Pregnant Women section notes as follows:

- There are no clinical studies of IFNβ-1b in pregnant women. The administration during confirmed pregnancy should be avoided, unless clearly needed.
- For a European study in women with MS who were treated with Interferon beta, the rates of adverse pregnancy outcomes were in line with reference ranges published in the literature.
- The Scandinavian registry study (see 3.2) has likewise not indicated an increased risk of congenital anomalies after pregnancy exposure to Interferon beta. However, the duration of exposure during the first trimester was uncertain since data were collected when Interferon beta use was contraindicated during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health.
- IFNβ-1b was not teratogenic at doses up to 0.42 mg (13.3 MIU)/kg/day in rhesus monkeys, but demonstrated dose-related abortifacient activity when administered at doses ranging from 0.028 mg to 0.42 mg/kg/day (2.8 to 40 times the recommended human dose based on body surface area comparison). It is not known if animal doses

can be extrapolated to human doses.

2.6 Australian package insert

2.6.1 IFNβ-1a

The Contraindications section specifies pregnant women or women who may be pregnant. The Fertility, Pregnancy and Lactation section notes as follows:

- IFNβ-1a was not teratogenic in rhesus monkeys at doses up to 50 μg/kg. Abortifacient activity was evident at 50 μg/kg but not at 1.25 μg/kg.
- There is limited information on the use of IFNβ-1a in pregnancy. In a US registry study (see 3.3), many of the 302 pregnant MS patients were exposed to IFNβ-1a during the first trimester (mean exposure 5.2 weeks). Exposure to IFNβ-1a did not increase the rate of spontaneous abortion or alter the pattern of defects compared to the general population. Due to the limitations of the study and absence of comparator MS population data, the significance of the observed spontaneous abortion rate is unclear.
- Initiation of treatment with IFNβ-1a is contraindicated during pregnancy. Women of child-bearing potential should take appropriate contraceptive measures during treatment with IFNβ-1a. If a patient becomes pregnant or plans to become pregnant while taking IFNβ-1a, the patient should be informed of the potential hazards to the foetus and it should be recommended that the patient discontinue therapy, unless the potential benefit justifies the potential risk to the foetus.

2.6.2 IFNβ-1b

Pregnant women or women who may be pregnant are not specified in the CONTRAINDICATIONS section. The Fertility, Pregnancy and Lactation section notes as follows:

- IFNβ-1b was not teratogenic in rhesus monkeys at doses up to 13.3 MIU/kg/day, but demonstrated an abortifacient activity when administered at doses ranging from 0.89 to 24 MIU/kg/day. It is not known whether IFNβ-1b can cause foetal harm when administered to a pregnant woman or can affect human reproductive capacity.
- Data from pregnancy registries and post-marketing experience on the use of IFNβ-1b suggest that frequencies of miscarriage and congenital abnormalities were comparable with the general population. Miscarriages have been reported in clinical trials with incidence rates not exceeding those in the general population. Therefore, women of

child-bearing potential should take appropriate contraceptive measures.

- If the patient becomes pregnant or plans to become pregnant while taking IFNβ-1b, she should be informed of the potential hazards and discontinuation of therapy should be considered; the benefits and possible risks of continuing IFNβ-1b therapy are recommended to be weighed.

3. Epidemiological studies in pregnant women

3.1 European registry study (J Neurol. 2020; 267:1715- 23)

A European registry study was performed to investigate their pregnancy outcomes in pregnant women who were administered with IFNβ-1a or IFNβ-1b[3]. Pregnant women who were administered with IFNβ-1a or IFNβ-1b during pregnancy or within 1 month before conception were enrolled in the study between April 1, 2009 and June 16, 2017. Data on pregnancy exposure were acquired prior to the knowledge of pregnancy outcome, or prior to the detection of a congenital anomaly at prenatal examination[4]. Spontaneously reported cases of HCP-confirmed pregnancies with a confirmed diagnosis of MS were included in the registry prospectively from the start of the study. In addition, after 2015, cases without a confirmed MS diagnosis, pregnancies not confirmed by an HCP, and solicited reports from prospectively identified patient support programs were also included.

Of the enrolled 2 447 cases, 948 cases with a known pregnancy outcome were included in the analysis. The prevalence of pregnancy outcomes was as follows in the Table 1: Spontaneous abortions represented 10.7% (101/948 cases), and congenital anomalies in live births 2.1% (17/794 cases)[5]. The authors discussed that the results were within the range of the incidence of spontaneous abortion (0 to 21.1%)[6] and congenital anomalies (0 to 8.9%)[7] already reported in the published literature regarding pregnant women with untreated MS.

[3] European IFN beta pregnancy registry
[4] No follow-up period is expressly noted.
[5] Congenital anomalies are defined as “morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not and include congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay, etc.” according to the definition in the Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (European Medicines Agency (EMA), 2005)
[6] Studies cited for the prevalence of spontaneous abortion in patients with untreated MS:
Mult Scler 2009; 15: 1037-42., Mult Scler 2016; 22 : 801-9., Neurology 2010; 75 : 1794- 802., Neurology 2005; 65 : 807-11., Neurology 2005; 65 : 802-6., Neurology 2005; 65 : 802-6., Mult Scler 2015; 21 : 198-205., Neurology 2014; 82 : 674-80., Neurol Ther 2015; 4 : 93-104., J Neurol 2008; 255 : 1250-3, BMC Neurol 2012; 12: 124, CNS Drugs 2010; 24 : 969-76.
[7] Studies cited for the prevalence of congenital anomalies in patients with untreated MS:
Mult Scler 2009; 15: 1037-42., Ther Adv Neurol Disord 2012; 5: 247-53., Mult Scler 2016; 22: 801-9., Neurology 2005; 65: 807-11., Neurology 2005; 65: 802-6., Mult Scler 2016; 22: 810-6., Mult Scler 2015; 21: 198-205., Mult Scler 2011; 18: 460-7., Mult Scler 2010; 16: 950-5.

Table 1 Pregnancy outcomes in the European IFN beta pregnancy registry

	Ectopic pregnancies	Spontaneous abortion	Elective termination (foetal defects)	Stillbirth with foetal defects	Stillbirth without foetal defects	Live birth with congenital anomaly*1
Number of events/n	4/948	101/948	6/948	1/948	2/948	17/794
Incidence (95% CI*2)	0.4 [0.12-1.08]	10.7 [8.76-12.79]	0.6 [0.23-1.37]	0.1 [0.00-0.59]	0.2 [0.03-0.76]	2.1 [1.05- 2.86]

*1: 794 live births of the 948 pregnancies with known outcomes were assessed for congenital anomalies.
*2: Confidence interval

Spontaneous abortion and live births with congenital anomalies were observed in 9.2% (38/412 pregnancies) and 0.7% (3/412), respectively, in the spontaneously reported cases. The prevalence was 10.7% (85/795) and 1.9% (15/795), respectively in the pregnancy cases with a confirmed diagnosis of MS, 11.4% (56/493) and 2.4% (12/493), respectively in the HCP-confirmed pregnancy cases. Authors discussed that no evidence for an adversely increased rate of congenital anomalies or spontaneous abortions was found in a specific population.

3.2 Scandinavian registry study (Ther Adv Neurol Disord. 2020; 13:1-15)

A registry-based study was conducted in Finland and Sweden with pregnant women with MS to investigate exposure or non-exposure before and during pregnancy to IFNβ-1a, IFNβ-1b, or peginterferon β-1a[8] and pregnancy outcomes[9]. Women listed in the MS registry from January 1, 1996 to December 31, 2014 in Finland and from July 1, 2005 to December 31, 2014 in Sweden with MS diagnosis and pregnancy outcomes (live birth, stillbirth, spontaneous abortion, elective termination, or ectopic pregnancy) were eligible. Background information, exposure to MS disease-modifying drugs (MSDMDs), and pregnancy outcomes were investigated and collected by linking data extracted from various registries[10] with a personal identification number. The follow-up period after birth was 12 months in Finland and 6 months in Sweden.

The incidence of pregnancy outcomes was calculated for each cohort in Table 2.

[8] In Finland and Sweden, peginterferon beta 1a was approved in July 2014 as indicated for MS.
[9] EUPAS13504 Study. Norway also joined when the study was planned but later was excluded due to a significant delay in the data access permission process.
[10] For MS diagnosis and drug exposure, data from the Drugs and Pregnancy Project, National Prescription Register, National Reimbursement Register, and Patient Register (Finland), the Prescription Registers and MS Register (Sweden) were integrated.

Table 2　Definitions of cohorts in EUPAS13504 study

Cohort 1	Pregnant women with MS exposed only to IFNβ[11]
Cohort 2	Pregnant women with MS exposed to IFNβ regardless of exposure to MS disease modifying drugs excluding IFNβ
Cohort 3	Pregnant women with MS unexposed to IFNβ and MSDMDs excluding IFNβ
Cohort 4	Pregnant women with MS unexposed to IFNβ regardless of exposure to MSDMDs excluding IFNβ

"Unexposed" is defined as no exposure for at least 3 months after the last menstrual period. Mitoxantrone and cladribine alone required 6 months of no exposure to be considered "unexposed."

2 831 pregnancy outcomes (1 074 in Finland, 1 757 in Sweden) were observed in 1 983 pregnant women with MS (755 in Finland, 1 228 in Sweden) during the study period.

The number and prevalence of the pregnancy outcomes were described for each cohort in Table 3.

Table 3 Pregnancy outcomes for each cohort in EUPAS 13504 Study

Pregnancy outcomes	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Total number of pregnancy outcomes	797	856	1 647	1 975
Ectopic pregnancies	1.6 (13/797)	1.5 (13/856)	3.2 (53/1 647)	3.1 (61/1 975)
Spontaneous abortions	8.3 (66/797)	8.1 (69/856)	12.0 (197/1 647)	11.2 (222/1 975)
Serious adverse pregnancy outcomes [a) b)]	2.2 (16/718)	2.2 (17/774)	4.0 (56/1 397)	3.7 (63/1 692)
Elective termination of pregnancy due to effects on pregnancy or foetal anomaly [b) c)]	0.7 (2/295)	0.7 (2/307)	0.8 (4/474)	0.7 (4/583)
Congenital anomalies in live birth [d)]	1.8 (12/666)	1.8 (13/722)	3.3 (44/1 330)	3.1 (49/1 605)
Still birth [b)]	0.3 (2/718)	0.3 (2/774)	0.6 (8/1 397)	0.6 (10/1 692)

Prevalence (%) (Events/all events assessed)
a) Serious adverse pregnancy outcome was defined as elective termination of pregnancy due to foetal anomalies, congenital anomalies in live births, and still births.
b) The denominator was defined as the total number of live births, still births, and elective terminations of pregnancy.
c) Swedish data were not available.
d) Congenital anomalies in live birth were defined as major congenital/foetal structural anomaly, chromosomal defect, teratoma, or hypothyroidism in live birth. The denominator was defined as the number of live births. Finnish data were not available for 2014.

Table 4 shows the relative risks of cohort 1 to cohort 3 in individual pregnancy outcomes. The authors concluded that no evidence was found to indicate that prevalence of the pregnancy outcomes was elevated among pregnant women exposed to only IFNβ[11] (cohort 1) compared to those unexposed to MSDMDs (cohort 3).

[11] In Table 4, "IFNβ" means IFNβ-1a, IFNβ-1b, or peginterferonβ-1a.

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Table 4 Relative risk of cohort 1 to cohort 3 for individual pregnancy outcomes in EUPAS 13504 Study

	Ectopic pregnancies	Spontaneous abortion	Profound effects on pregnancy	Elective termination of pregnancy due to effects on pregnancy or foetal defects [b)]	Congenital anomalies in live birth [c)]	Still births
Relative risk [a)] (95% CI)	0.53 [0.29-0.98]	0.78 [0.60-1.02]	0.55 [0.31-0.96]	1.94 [0.35-10.85]	0.52 [0.27-0.99]	0.41 [0.09-1.93]

a) Log-binomial regression was performed using country, year of pregnancy outcome, maternal age at the last menstrual period (LMP), number of previous pregnancies, any chronic diseases, and exposure to any teratogenic medications including steroids as covariates.
b) Swedish data were not available on elective termination.
c) Finnish data were not available on 2014.

3.3 US Registry study (C-871 Study)

A registry study was performed in the US in pregnant women with MS who were exposed to IFNβ-1a to investigate the prevalence of spontaneous abortions and congenital anomalies. Between March 3, 2004 and September 8, 2011, pregnant women with MS exposed to IFNβ-1a within approximately 1 week after conception or during the first trimester of pregnancy were enrolled and followed up until 8 to 12 weeks after delivery together with born infants.

Of the 321 women enrolled before a prenatal examination that could detect information related to pregnancy outcomes or after one that detected no anomalies, 302 women were included in the analysis population, excluding 19 (9 lost to follow-up and 10 considered not valid for reasons such as not being confirmed by the health care provider). 266 women were enrolled before they became 22 weeks pregnant, and 10.5% (28/266) of them experienced spontaneous abortion. The prevalence was comparable to that (16%)[12] in the US general population which was comprised of pregnant women with or without MS, and that (9.8%)[13] in those with untreated MS as reported in the literature.

In addition, of the 272 live births including 4 twin pregnancies, congenital anomalies[14]

[12] J R Soc Health 1987; 107: 31-3., Natl Vital Stat Rep 2009 14; 58: 1-14.
[13] Mult Scler 2009;15: 1037-42
[14] 14. Congenital anomalies are defined as follows
(1) Any significant structural or chromosomal defect diagnosed with signs/symptoms using the CDC MACDP classification of birth defects.
(2) Any case with two or more secondary or 'conditional' abnormalities that would not have been classified as primary birth defects by the CDC MACDP (determined subject to the agreement between the raters and the advisory committee.)
(3) Any signs and symptoms falling under (1) or (2) in spontaneously aborted babies, foetuses, or stillborn infants detected by regular or prenatal examinations(determined subject to the agreement between the raters and the advisory committee.)
The following signs and symptoms are excluded from congenital anomalies.
・Those noted during gestation shorter than 36 weeks (including unknown duration of gestation) or in live infants with a

presented in 6.3% (17/272 cases, [95%CI:3.8-10.0, Fleiss test[15] (1981)]) with a statistically significant difference compared with the prevalence of congenital anomalies (2.7%) in the general population in the Metropolitan Atlanta Congenital Defects Program (MACDP)[16].

4. Japanese and overseas clinical practice guidelines, standard textbooks, or published literature

4.1 Japanese and overseas clinical practice guideline

4.1.1 Japanese guidelines

Clinical Practice Guidelines for Multiple Sclerosis and Optic **Neuromyelitis (Japanese Society of Neurology 2017, hereinafter referred to as the "Japanese guideline")**

The Japanese guideline states as follows regarding the use of Interferon beta in pregnant women.

In Japan, the use of Interferon beta in pregnant women is contraindicated. Patients receiving Interferon beta should be instructed to use proper contraception. Overseas cohort studies reported that the rates of preterm birth, lower mean birth weight, shorter mean birth length, and preterm birth earlier than 37 weeks of gestation were significantly higher in the group of women exposed to Interferon beta during pregnancy compared to the non-exposed group but that the rates of congenital malformation and spontaneous abortion were not significantly different[17] between the 2 groups. No adverse events were noted in a Japanese clinical study[18]. The Japanese guideline proposes, based on the study in which no adverse events were observed with exposure to Interferon beta up to 1 month pregnancy, for patients on Interferon beta for MS with high disease activity that they should be carefully monitored for signs of pregnancy and immediately discontinue Interferon beta once pregnancy is confirmed[19].

birth weight lower than 2 500 g.
・Those noted in infants susceptible to infection or with anomalies due to biochemical abnormalities are handled as without congenital anomalies unless there is a possibility of a specific congenital anomaly.
・Signs or symptoms noted prior to 20 weeks of gestation.

[15] Statistical Methods for Rates and Proportions, Third Edition. Joseph L. Fleiss et al.
[16] A program for researchers to investigate and track all congenital anomalies in the subject community to ascertain the prevalence of congenital anomalies in the community population.
[17] Neurology 2012; 79: 1130-5
[18] Clinical and Experimental Neuroimmunology 2015; 6:402-8
[19] Neurology 2010; 75: 1794-1802.

4.1.2 The US guideline

Practice guideline: Disease-modifying therapies for adults with multiple sclerosis (American Academy of Neurology, 2018, hereinafter referred to as the "US guideline").

The US guideline prepared by the American Academy of Neurology refers to a description in the US package insert that IFNβ should be used in pregnancy only if the potential benefit justifies risk to the foetus.

4.1.3 European guideline

ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis (European Committee of Treatment and Research in Multiple Scolerosis/ European Academy of Neurology, 2018, hereinafter referred to as the "European guideline").

The European guideline prepared by the European Committee of Treatment and Research in Multiple Scolerosis/European Academy of Neurology state as follows regarding the use of Interferon beta in pregnant women:

A study indicated no significant difference between groups exposed or unexposed to Interferon beta in the proportion of infants born with low birth weight (see 4.3.2.3)[20]. This was confirmed with 2 additional studies of lower accuracy reporting similar results (see 4.3.2.10, 4.3.2.11). Regarding spontaneous abortion, a study has been reported to find that spontaneous abortion occurred in a higher proportion in the group of women exposed to Interferon beta than in the group of women unexposed (see 4.3.2.3, 4.3.2.8, 4.3.2.10, 4.3.2.11)[21]. For the prevalence of congenital malformations, only smaller studies have been reported from which no consistent findings have been retrieved.

・For women planning a pregnancy, if there is a high risk of disease reactivation, using Interferon beta or glatiramer acetate may be considered until pregnancy is confirmed. In some very specific cases with very high activity, continuing this treatment during pregnancy could also be considered.

[20] Subjected to the Cochrane Risk Of Bias In Non-randomized Studies – of Interventions tool for the degree of bias, this study was determined to be of moderate bias.
[21] Noted as of not good quality due to the small size of subjects.

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4.2 Major textbooks

4.2.1 Williams Obstetrics, 25th Edition (Cunningham FG, et al., 2018)

DMDs are used for relapsing MS or for exacerbations during pregnancy. IFNβ-1a, IFNβ-1b, and glatiramer may lower relapse rates by a third. Data concerning safety in pregnancy are limited but overall reassuring. In a review of 35 pregnancies, first trimester drug exposure did not worsen outcomes.

4.2.2 Handbook of Neurology 5th edition: Differential diagnosis and treatment (Yoshikuni Mizuno, 2016)

Interferon beta is not teratogenic. While low birth-weight infants, foetal death, stillbirth, spontaneous abortion, small for 2 years of age have been reported in patients exposed to the drug up to 4 weeks of conception, the risk of congenital malformation is small.

4.2.3 Merritt’s Neurology, 14th edition (Louis ED, et al., 2021)

Interferon beta is the safest option among MSDMDs. No effects related to spontaneous abortion have been reported. Exposure in the first trimester of pregnancy is safe.

4.2.4 Harrison's Principles of Internal Medicine, 20th edition (Jameson JL, et al., 2018)

Although the risk of adverse reactions in the administration of Interferon beta and glatiramer is considered to be low, administration of MSDMDs is usually discontinued in pregnant women.

4.2.5 UpTo Date, Indications for switching or stopping disease-modifying therapy for multiple sclerosis (Olek MJ, et al., 2020)

For women who desire to become pregnant, the risk of possible adverse effects of MSDMDs on the foetus must be weighed against MSDMDs discontinuation and increased risk of maternal disease relapses. In addition, certain MS drugs are known for their teratogenicity, and a causal relationship between IFNβ and teratogenicity is reasonably possible.

4.3 Published literature

Representative literature published regarding the use of IFNβ in pregnant women is as follows[22].

4.3.1 Systematic review

4.3.1.1 Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review (Neurology. 2012; 79: 1130-5)

A systematic review was performed to examine the effects of the perinatal use of IFNβ, glatiramer, natalizumab (genetical recombination), mitoxantrone or fingolimod on developmental outcomes in offspring of patients with MS. 15 studies (4 prospective cohort studies, 5 retrospective cohort studies, and 6 case studies) were included in the review.

Among the studies evaluated, those with IFNβ revealed no consistent findings regarding mean birth weight, mean duration of gestation, preterm birth, and spontaneous abortions. The rates of spontaneous abortions, cesarean section, or low mean birth weight were not associated with IFNβ exposure in studies of the highest quality (4.3.2.8). In the other studies of not-high quality, no associations were found between IFNβ exposure and mean duration of gestation or congenital anomalies. The rates of therapeutic abortion were higher in the group exposed to IFNβ compared to the non-exposed group, and lower compared to the general population.

4.3.2 Cohort studies

4.3.2.1 Pregnancy outcome following first-trimester exposure to fingolimod: A collaborative ENTIS study (Mult Scler. 2021; 27: 475-8)

A prospective cohort study in women exposed in the 1st trimester of pregnancy to Interferon beta (62 events) or to fingolimod (63 events) was performed. Among the pregnancies with a reported pregnancy outcome, rates of major congenital anomalies were 2.3% (1/44 births) in the Interferon beta exposed group versus 4.8% (2/42 births) in the fingolimod exposed group, the latter revealing no statistically significant differences

[22] Of the published literature collected using PubMed with search formula (("avonex" OR "betaferon" OR "extavia" OR "plegridy" OR "rebif" OR "betaseron" OR "*interferon-beta*" OR "*interferon beta*" OR "*beta interferon*" OR "*beta-interferon*") AND ("pregnan*" OR "teratogen*" OR "genotoxic*" OR "mutagen*" OR "abort*" OR "congenit*" OR "birth defect*" OR "fetal") AND "multiple sclerosis"), and using Ichushi with search formula (("Interferon Beta-1a"/TH or アボネックス/AL) or ("Interferon Beta-1b"/TH or ベタフェロン/AL)or (Interferon-Beta/TH or インターフェロン　ベータ/AL)) and ((妊娠/TH or 妊娠/AL) or (妊産婦/TH or 妊婦/AL) or (先天奇形/TH or 奇形/AL) or (遺伝毒性/TH or 遺伝毒性/AL) or (変異誘発/TH or 変異原性/AL) or (流産/TH or 流産/AL) or 先天/AL or (胎児/TH or 胎児/AL)) and (多発性硬化症/TH or 多発性硬化症/AL), those on studies of IFNβ in pregnant women published between 2005 and 2021 was retrieved. (searched on April 27, 2021)

compared to the Interferon beta exposed group (odds ratio, 2.2; 95% confidence interval, 0.2–24.6). The rates of spontaneous abortion were 17.7% (11/62 events) in the interferon-β exposed group versus 11.1% (7/63 events) in the fingolimod group, revealing no statistically significant differences (adjusted hazard ratio 0.6; 95% confidence interval, 0.2–1.8).

4.3.2.2 Pregnancy decision-making in women with multiple sclerosis treated with natalizumab:I:Fetal risks (Neurology 2018; 90:e823-31)

In Italy, foetal risks in pregnant women with MS exposed to natalizumab (genetical recombination) (69 cases) were retrospectively assessed compared to those with MS exposed to Interferon beta (88 cases) and to those with untreated MS (341cases). The rate of major congenital anomalies was 2.9% (2/69 events) in the natalizumab (genetical recombination) exposure group, 1.1% (1/88 event) in the Interferon beta exposure group, and 0.9% (3/341 events) in the untreated group, with no significant differences noted among the 3 groups. The rate of spontaneous abortions was 17.4% (12/69 events) in the natalizumab (genetical recombination) exposure group, 8.0% (7/88 events) in the Interferon beta exposure group, and 6.5% (22/341 events) in the untreated group. Multivariate analysis identified natalizumab (genetical recombination) exposure as a significant risk factor of spontaneous abortions.

4.3.2.3 Interferon beta exposure during first trimester is safe in women with multiple sclerosis—A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry (Mul Scler. 2016; 22: 801-9) 801-9)

A registry study was conducted in Germany on 251 pregnancies that were exposed to Interferon beta (exposed group) and 194 pregnancies that were unexposed to MSDMDs (unexposed group) both after LMP. No statistically significant differences were observed between the exposed and unexposed groups regarding birth weight (mean ± standard deviation) (exposed: 3 272.28 ± 563.61 g; unexposed: 3 267.46 ± 609.81 g, p = 0.935: paired t-test), birth length (mean ± standard deviation) (exposed: 50.73 ± 3.30 cm; unexposed: 50.88 ± 3.45 cm, p = 0.669: two-sided t-test), prevalence of preterm birth (exposed: 6.61%; unexposed: 9.94%, p = 0.187: Fisher's exact test), prevalence of spontaneous abortion (exposed: 9.56%; unexposed: 6.70%, p = 0.304: Fisher's exact test), and prevalence of congenital anomalies (exposed: 3.08%; unexposed: 5.52%,p = 0.197: Fisher's exact test).

4.3.2.4 Pregnancy outcomes in Lebanese women with multiple sclerosis (the LeMS study): a prospective multicentre study (BMJ Open. 2016; doi:10.1136/ bmjopen 2016-011210) 10.1136/ bmjopen 2016-011210)

A prospective cohort study was conducted in medical centers in Lebanon with women before pregnancy with a history of MS to assess the frequency of MS relapse and pregnancy outcome, and 64 pregnancy outcomes were collected in 29 women. All women received INFβ-1a and stopped the treatment by 3 months before conception. All deliveries resulted in normal birth with no congenital anomalies observed.

4.3.2.5 Final results from the Betaseron (interferon β-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events. (BMJ Open. 2014; doi: 10.1136/bmjopen-2013-004536)

A registry study was conducted in the US with pregnant women for whom exposure to INFβ-1b started after LMP or during pregnancy to evaluate the rates of spontaneous abortion and congenital anomalies. Among the pregnancies with reported outcomes, the prevalence of spontaneous abortion was 11.5% (11/96 events) and was not significantly different from the prevalence of 16% from the National Survey of Family Growth (relative risk 0.7 (95% CI 0.4 to 1.2), p=0.86; Fisher's exact test). The birth defect rate among the live births was 5.8% (5/86 live births) and was not significantly different from that reported for the general population by the MACDP (2.78%) (relative risk 2.1 (95% CI 0.9 to 4.9), p=0.092; Fisher's exact test).

4.3.2.6 Multiple sclerosis and pregnancy: experience from a nationwide database in Germany (Ther Adv Neurol Disord. 2012; 5:247-53)

A study using a database was performed in Germany in MS patients with the objective to evaluate the influence of exposure to MSDMDs during pregnancy on their pregnancies and breastfeeding. Congenital anomalies were observed in 3.8% (3/78 events) in the Interferon beta-exposed group, 4.9% (2/41 events) in the glatiramer exposure group, and 3.2% (7/216 events) in the MSDMDs non-exposure group.

4.3.2.7 Perinatal outcomes in women with multiple sclerosis exposed to disease-modifying drugs (Mult Scler. 2012; 18:460-7)

An analysis was conducted by linking 2 Canadian MS databases, the British Columbia

(BC) MS database and the BC Perinatal Database Registry to investigate the pregnancy outcomes. No congenital anomalies were identified in 21 pregnancies exposed to MSDMDs from 1 month prior to and during pregnancy (including 15 pregnancies exposed to Interferon beta).

4.3.2.8 Pregnancy and fetal outcomes after Glatiramer Acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study (BMC Neurol 2012; 12: e823-31), Pregnancy and fetal outcomes after interferon beta exposure in multiple sclerosis (Neurology. 2010; 75:1794-802)[23]

A prospective cohort study was conducted in Italy with pregnancies exposed to Interferon beta (Interferon beta exposed group, 88 events) and those not exposed to MSDMDs (MSDMDs non-exposed group, 318 events). Among the pregnancies with reported pregnancy outcomes, spontaneous abortions occurred in 7.95% (7/88 events) in the Interferon beta exposed group, showing no significant statistical differences compared to 6.29% (20/318 events) in the non-exposure group (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.4 to 2.9, p = 0.88, Mann Whitney U test). Significant differences were observed in birth weight (mean ± SD) (exposed group 3 010 ± 513 g, non-exposed group 3 209 ± 488 g) and birth length (mean ± SD) (exposed group 48.7 ± 3.4 cm, non-exposed group 49. 9 ± 3.2 cm) (p<0.036, p = 0.014, respectively, Mann Whitney u test). In the median 2.1 years of follow-up or longer, no serious foetal complications, congenital anomalies, or malformations were observed.

4.3.2.9 Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study (Mult Scler. 2009; 15: 1037-42)

A cohort study was performed in Germany in which pregnancy outcomes of women with MS who were exposed to MSDMDs (glatiramer, IFNβ-1a, IFNβ-1b) were investigated in comparison to a group of pregnant women with untreated MS and that of pregnant women without MS. Major birth defects[24] were observed in 7.7% (2/26 events) of the glatiramer exposed group, in 0% (0/40 events) of the IFN-β1a exposed group, 0% (0/14 events) of the IFN-β1b exposed group, 5.3% (3/57 events) of the MSDMDs non-exposed group, and 1.6% (23/1 405 events) of the non-MS group. Spontaneous abortions[25] were observed in 3.9%

[23] 2 articles are collectively summarized because they report studies using the same data set.
[24] Cases of elective terminations with malformations are included.
[25] Cases of elective terminations were excluded.

(1/26 event) of the glatiramer exposed group, 4.8% (2/42 events) of the IFNβ-1a exposed group, 27.8% (5/18 events) of the IFN-β1b exposed group, 9.8% (6/61 events) of the MSDMDs non-exposed group, and 9.1% (138/1515 events) of the non-MS group. The IFNβ-1b exposed group showed significant differences compared to the glatiramer exposed group, IFNβ-1a exposed group, and the non-MS group (p = 0.03, p= 0.02, p= 0.02, respectively, Cochrane–Mantel–Haenszel test).

4.3.2.10 Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? (J Neurol. 2008; 255: 1250-3)

Regarding pregnant women with MS who were exposed to Interferon beta in their early pregnancy in Italy, a cohort study was performed to compare their pregnancy outcomes with those for women exposed to Interferon beta only prior to conception and those for women not exposed to Interferon beta. No malformations were identified in any cases. Spontaneous abortions were observed in 7.1% (1/14 case) of the Interferon beta early pregnancy exposure group, 0% (0/7 cases) of the Interferon beta prior to conception only exposure group, and 5.9% (1/17 case) of the Interferon beta non-exposed group.

4.3.2.11 The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort (Neurol. 2005; 65: 807-11)

A cohort study was performed to assess the reproductive risks (23 pregnancies) in 16 pregnant women with MS, etc.[26] in Canada who were exposed to IFNβ during pregnancy in comparison with a group of pregnant women with MS unexposed to IFNβ (21 cases) and a group of healthy pregnant women (20 cases). Major malformations were identified in 8.7% (2/23 events) of the IFNβ exposed group, 4.8% (1/21 event) of the IFNβ non-exposed group, and 5.0% (1/20 event) of the healthy pregnant women group. Spontaneous abortions were observed in 39.1% (9/23 events) of the IFNβ exposed group, 19.0% (4/21 events) of the IFNβ non-exposed group, and 5.0% (1/20) of the healthy pregnant women group. The IFNβ exposed group showed a significant difference compared to the healthy pregnant women group (p= 0.032, Wald test).

[26] 14 cases of MS, 1 case of increased platelet counts, 1 case of essential thrombocythemia

4.3.3 Assessment with pharmacovigilance databases and clinical trials

4.3.3.1 Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure (Ther Adv Neurol Disord. 2020; doi: 10.1177/1756286420910310)

Outcomes of pregnancies were reviewed based on a pharmacovigilance (PV) database for IFNβ-1b from worldwide sources (January 1995 to February 2018). Of the pregnancies with their pregnancy outcomes unknown at the time of reporting to the database and known thereafter, spontaneous abortions were observed in 11.9% (160/1 348 events). Congenital anomalies were observed in 1.4% (14/981 events) of live births, comparable to the rates (2.8% and 2.4%) of the MACDP and the European Surveillance of Congenital Anomalies[27] (hereinafter referred to as the “EUROCAT”).

4.3.3.2 Pregnancy outcomes in patients exposed to interferon beta-1b (J Neurol Neurosurg Psychiatry. 2015; 86: 587-9)

Outcomes of pregnancies were reviewed based on a pharmacovigilance (PV) database for IFNβ-1b from worldwide sources (up to July 2013). Of the pregnancies with their pregnancy outcomes unknown at the time of reporting to the database and known thereafter, spontaneous abortions were observed in 14.4% (61/423 events), comparable to the rates (12 to 15%)[28] in the general population and those in the US (15 to 16%)[29]. Birth defects were observed in 1.9% (8/423 events) of pregnancy outcomes, comparable to the rates (3% and 2%, respectively) of the MACDP and the EUROCAT.

4.3.3.3 Outcomes of pregnancy during interferon beta-1a therapy in Japanese patients with multiple sclerosis: Interim results of a postmarketing surveillance study (Clinical and Experimental Neuroimmunology 2015; 6:402-8)

Pregnancy outcomes were evaluated in the post-marketing surveillance study of IFNβ-1a in Japan (November 8, 2006 to December 2, 2010). A total of 1 638 patients were registered in the study, including 1 110 women. A total of 21 pregnancies were reported, with 1 resulting in spontaneous abortion but none with congenital anomalies.

[27] The European network of population based registers to provide essential epidemiological information on congenital anomalies in Europe, facilitates the early warning of emerging teratogenic factors, evaluates the effectiveness of primary prevention.
[28] Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14: 839–54.
[29] Stud Fam Plann 2007; 38: 187–97.

4.3.3.4 Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy (Mult Scler. 2011; 17: 423-30)

Reproductive risks were evaluated using a global pharmacovigilance (PV) database for IFNβ-1a (February 1998 to November 2009). Of the pregnancies reported to the database prospectively with their outcomes unknown and pregnancies reported retrospectively when their outcomes were known, subsequent outcomes were reported in 425 and 254 pregnancies, respectively. The prevalence of spontaneous abortions in the prospectively and retrospectively reported pregnancies was 11.5% (49/425 events) and 37.8% (96/254 events), and the prevalence of birth defects in the live births was 1.2% (4/328 events) and 3.8% (5/131 events).

4.3.3.5 Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis (Neurol. 2005; 65: 802-6)

Risks associated with IFNβ-1a in pregnancy were investigated using data from 8 clinical trials with IFNβ-1a. The rate of congenital anomalies was 2.4% (1/41 event) in the IFNβ-1a in utero exposure group, 4.5% (1/22 event) in the IFNβ-1a previous exposure group, and 16.7 % (1/6 event) in the placebo group. Foetal death was observed in 2.4% (1/41 event) in the IFNβ-1a in utero exposure group, 0% (0/22 events) in the IFNβ-1a previous exposure group, and 0% (0/6 events) in the placebo group. Spontaneous abortion was observed in 39.1% (8/41 events) in the IFNβ-1a in utero exposure group, 0% (0/22 events) in the IFNβ-1a previous exposure group, and 0% (0/6 events) in the placebo group. Congenital anomalies, foetal death, and spontaneous abortions were observed only in the IFNβ-1a in utero exposure group.

5. Current description of the Japanese package inserts of MSDMDs

Of the MSDMDs that are indicated for prevention of relapse or delaying progression in MS, fingolimod hydrochloride and siponimod fumarate are contraindicated for administration to pregnant women or women who may be pregnant. Natalizumab (genetical recombination), dimethyl fumarate, glatiramer, and ofatumumab (genetical recombination) should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks.

6. Adverse reaction reports and use-results surveys in Japan

Up to August 31, 2021, 4 events in 3 cases of adverse reactions related to congenital anomalies[30] (stillbirth, spontaneous abortion, threatened labour, and placenta praevia) had been reported in pregnant women exposed to IFNβ-1a or IFNβ-1b. A causal relationship between IFNβ-1a or IFNβ-1b and the event could not be established in any of these cases. No foetal or neonatal malformations had been reported as adverse reactions (Appendix 3).

The IFNβ-1a use-results survey had collected 1 510 cases and among 17 pregnant women with MS, 1 case each of spontaneous abortion and elective termination of pregnancy was reported (re-examination report with Avonex IM Injection PEN 30 μg, Avonex IM Injection Syringe 30 μg dated February 1, 2018). The IFNβ-1b use-results survey had collected 1 371 cases and among 14 pregnant women with MS, 1 case of caesarean section due to placenta praevia was reported (re-examination report of Betaferon for SC injection 960 IU, dated May 14, 2013). Some cases and events in the adverse reaction reports and the use-results survey in Japan overlap.

7. Research papers and reported foreign measures

Up to August 31, 2021, 4 studies related to congenital abnormalities in pregnant women administered with IFNβ-1a or IFNβ-1b were identified (Appendix 4). Meanwhile, no foreign measures related to congenital anomalies in pregnant women administered with IFNβ-1a or IFNβ-1b had been reported as of August 31, 2021.

8. PMDA's judgement based on the investigation results

PMDA considers, for the following reasons, that "pregnant women or women who may be pregnant" may be deleted from the CONTRAINDICATIONS section in the precautions for IFNβ, and replaced with a cautionary statement that pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks.

- Although foetal death or spontaneous abortions were observed in reproductive toxicity studies in monkeys with IFNβ-1b or IFNβ-1a, the blanket contraindication of IFNβ in pregnant women or women who may be pregnant based on these studies is not considered substantially required according to the current understanding (of

[30] Events falling under SOC's "pregnancy, puerperium and genetic disorders" or SOC's "congenital, familial and genetic disorders" and observed after the suspect drug was administered to the mother.

reproductive toxicity) in the following respects.

- With IFNβ-1b, the serum IFN level was below the lower limit of quantitation at the majority of timepoints in MS patients single-dosed at 1.6 or 8 MIU[31] and, therefore, exposure levels cannot be compared between humans and monkey. Nonetheless, foetal deaths and spontaneous abortions were not observed at 119 times human clinical dose (40 times based on body surface area [mg/m^2] comparison), starting to emerge at 200 times human clinical dose (67 times [mg/m^2])[32].
- With IFNβ-1a, although exposure levels were not measured in the reproductive toxicity studies, based on the AUCs in monkeys single-dosed with 10 MIU/kg in nonclinical pharmacokinetic studies, the exposure levels of the group dosed at 10 MIU/kg on an alternate-day subcutaneous basis, which is the dosage and administration when spontaneous abortions were observed in the reproductive toxicity studies, are considered comparable to 83 to 163 times the exposure level of healthy adults intramuscularly single-dosed 31.5 μg (AUC 384 IU・hr/mL). Although no data are available to estimate the exposure level of the group alternate-day subcutaneously dosed at 0.25 MIU/kg, in which cases of abortion were observed in the reproductive toxicity studies in monkeys, the dose is comparable to 5.8 times the human clinical dose (1.9 times [mg/m^2]).

• There have not been consistent assessments regarding administration of IFNβ in pregnant women or women who may be pregnant as indicated as follows and, therefore, the current contraindication should not necessarily be maintained.

- The European, Scandinavian, and US registry studies in pregnant women with MS administered with IFNβ, as well as other epidemiological studies and literature reports have not necessarily suggested the possibility of an increase in the risks of spontaneous abortions and congenital anomalies.
- The Australian package inserts contraindicate administration of IFNβ-1a to pregnant women while the US package inserts do not contraindicate but recommend administration of IFNβ with potential benefits against expected risks considered. The EU package insert had initially placed at the time of initial approval but later

[31] Betaferon review report

[32] In the animal study conducted for marketing approval of IFNβ-1b in which IFNβ-1b was subcutaneously administered to pregnant rhesus monkeys during the period of organogenesis or 20 to 70 days of gestation, increased rates of spontaneous abortion or foetal death were observed in the group at 13.4 MIU/kg/day or higher and the NOAEL to maternal reproductive function and the foetuses was determined to be 8 MIU/kg/day. 8 MIU/kg/day and 13.4 MIU/kg/day are 40 times and 67 times [mg/m2] the human clinical dose of approximately 5.4μg/kg, respectively.

lifted contraindication of IFNβ (in pregnant women) in 2019 based on the results of the registry studies mentioned above. Thus, opinions of foreign regulatory authorities vary regarding administration in pregnant women. In addition, the EU guideline already stated prior to the lifting of contraindication in the EU that administration of IFNβ may be considered as a therapy in pregnant women.

- The Japanese guideline states that declined relapse rates during pregnancy or early postpartum have been reported in pregnant women with MS who continued MSDMDs up to their first trimester compared with the group of pregnant women with untreated MS. This is considered to indicate that allowing administration of IFNβ would add a treatment option for prevention of MS relapse early postpartum, thereby having a certain medical significance.

VI. Expert Discussion

The above opinions by PMDA were supported by expert advisors with their own opinions, such as that contraindication against pregnant women or women who may be pregnant should be lifted, taking into account that discontinuing MSDMDs including IFNβ in women with MS who are or may be pregnant may increase the risk of relapse of the disease during pregnancy and that the relapse during pregnancy has been reported[33] as a risk of long-term disability worsening.

IV. Overall evaluation

Based on the discussion above, PMDA concluded that precautions in the package inserts may be revised as Appendix 5 and 6. (Appendix 5 and 6 are not included here. See the Detailed information on Revisions of PRECAUTIONS.)

[33] Mult Scler. 2021 Jun 16;13524585211023365.

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix 1

Descriptions in overseas package inserts (Avonex)

US package insert (the March 2020 version)	**4. CONTRAINDICATIONS** <No related description> **8. USE IN SPECIFIC POPULATIONS** 8.1 Pregnancy <u>Risk Summary</u> 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). In a study in pregnant monkeys, administration of interferon beta during pregnancy resulted in an increased rate of abortion at doses greater than those used clinically (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. <u>Data</u> <u>Human Data</u> 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 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. 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. Animal Data In pregnant monkeys given interferon beta at 100 times the recommended weekly human dose (based upon a body surface area [mg/m^2] comparison), no adverse effects on embryofetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. No abortifacient effects were observed in monkeys treated at 2 times the recommended weekly human dose (based upon mg/m^2).
EU package insert (the March 2021 version)	**4.3 Contraindications** <No related description> **4.6 Fertility, pregnancy and lactation** Pregnancy

	A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited. Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far. If clinically needed, the use of Avonex may be considered during pregnancy.
German package insert (the February 2021 version)	**4.3 Gegenanzeigen** <No related description> **4.6 Fertilität, Schwangerschaft und Stillzeit** Schwangerschaft Weitreichende Erfahrungen (mehr als 1000 Schwangerschaftsausgänge) aus Registern und nach Markteinführung deuten nicht auf ein erhöhtes Risiko für schwerwiegende angeborene Fehlbildungen nach Exposition mit Interferon beta vor der Empfängnis oder im ersten Schwangerschaftstrimenon hin. Die Expositionsdauer während des ersten Trimenons ist jedoch nicht genau bekannt, da die Daten zu einem Zeitpunkt erhoben wurden, als die Anwendung von Interferon beta während der Schwangerschaft kontraindiziert war und die Behandlung wahrscheinlich unterbrochen wurde, als eine Schwangerschaft festgestellt und/oder bestätigt wurde. Die Erfahrungen mit einer Exposition während des zweiten und dritten

	Schwangerschaftstrimenons sind sehr begrenzt. Basierend auf Daten aus Tierstudien (siehe Abschnitt 5.3) besteht ein potenziell erhöhtes Risiko für Spontanaborte. Das Risiko von Spontanaborten bei mit Interferon beta exponierten Schwangeren kann anhand der derzeit vorliegenden Daten nicht hinreichend bewertet werden, aber die Daten weisen bisher nicht auf ein erhöhtes Risiko hin. Falls klinisch erforderlich, kann die Anwendung von AVONEX während der Schwangerschaft inBetracht gezogen werden.
French package insert (the October 2019 verseion)	**4.3 Contre-indications** <No related description> **4.6 Fertilité, grossesse et allaitement** <u>Grossesse</u> Un grand nombre de données (plus de 1000 grossesses) issues de registres et de la surveillance post-commercialisation n'a pas mis en évidence un risque augmenté de malformations congénitales majeures après une exposition à l'interféron bêta précédant la conception ou au cours du premier trimestre de grossesse. Néanmoins, la durée d'exposition au cours du premier trimestre est incertaine car les données ont été recueillies alors que l'utilisation de l'interféron bêta était contre-indiquée pendant la grossesse, et le traitement a probablement été interrompu lorsque la grossesse a été détectée et/ou confirmée. Les données concernant l'exposition durant le deuxième et le troisième trimestres de la grossesse sont très limitées. D'après les données chez l'animal (voir rubrique 5.3), le risque d'avortement spontané pourrait être augmenté. Les données actuellement disponibles chez les femmes enceintes exposées à l'interféron bêta ne permettent pas d'évaluer correctement le risque d'avortement spontané, mais ces donnéesà ce jour, ne suggèrent pas d'augmentation de ce risque. Si l'état clinique de la patiente le nécessite, l'utilisation d'Avonex peut

	être envisagée pendant la grossesse.
Canadian package insert (the May 2020 version)	CONTRAINDICATIONS <No related description> Special Populations Pregnant Women: The extent of exposure in pregnancy during clinical trials is:limited: < 1000 pregnancies There are no adequate and well-controlled studies of AVONEX PS/AVONEX PEN in pregnant women. The administration of AVONEX PS/AVONEX PEN during confirmed pregnancy should be avoided, unless clearly needed. A European registry study collected data on 948 prospective pregnancies in women with MS who were treated with one of five interferon beta medications. The rates of aggregated adverse pregnancy outcomes were in line with reference ranges published in the literature. Data from a prospective pregnancy registry that included 302 MS patients exposed to Avonex in the United States found an increased incidence of major birth defects compared to a reference population. Data from a retrospective register-based study in Sweden and Finland have not indicated an increased risk of major congenital anomalies after early pregnancy exposure to drugs in the interferon beta class. Given these contrasting data, it is unclear whether Avonex has teratogenic effects. In each of the studies discussed above, the duration of exposure during the first trimester was uncertain since data were collected when interferon beta use was contraindicated or strongly advised against during pregnancy, and treatment was interrupted when the pregnancy

	was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health. The reproductive toxicity of AVONEX PS/AVONEX PEN has been studied in animals. In pregnant monkeys given AVONEX at 100 times the recommended weekly human dose (based upon body surface area comparison), no teratogenic effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. These effects are consistent with the abortifacient effects of other type I interferons. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot be evaluated based on the currently available data.
Australian package insert (the February 2021 version)	4.3 CONTRAINDICATIONS AVONEX is contraindicated in patients with current severe depression and/or suicidal ideation and in women who are or plan to become pregnant while on therapy. 4.6 FERTILITY, PREGNANCY AND LACTATION Use in pregnancy – Category D Interferon beta-1a was not teratogenic in rhesus monkeys at doses up to 50 µg (10 million IU)/kg SC. Abortifacient activity was evident at this dose but not at 1.25 µg (0.25 million IU)/kg. Patients should be advised of the abortifacient potential of interferon beta observed in animal studies. There is limited information on the use of AVONEX in pregnancy. In a pregnancy registry, 302 pregnant MS patients exposed to AVONEX, primarily during the first trimester (mean exposure 5.2 weeks) were followed prospectively. Exposure to AVONEX did not increase the rate of spontaneous abortion or alter the pattern of defects compared to the general population. Due to the limitations of the study and absence

	of comparator MS population data the significance of the observed spontaneous abortion rate is unclear. Initiation of treatment is contraindicated during pregnancy (see Section 4.3 - Contraindications). Women of child-bearing potential should take appropriate contraceptive measures during treatment with AVONEX. If a patient becomes pregnant or plans to become pregnant while taking AVONEX, the patient should be informed of the potential hazards to the foetus and it should be recommended that the patient discontinue therapy, unless the potential benefit justifies the potential risk to the foetus.

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Appendix 2

Descriptions in overseas package inserts (Betaferon)

US package insert (the October 2020 version)	**4. CONTRAINDICATIONS** <No related description> **8. USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** *Risk Summary* Although there have been no well-controlled studies in pregnant women, available data, which includes prospective observational studies, have not generally indicated a drug-associated risk of major birth defects with interferon beta-1b during pregnancy. Administration of BETASERON to monkeys during gestation resulted in increased embryo-fetal death at or above exposures greater than 3 times the human therapeutic dose (see Animal Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown. *Data* <u>Human Data</u> The majority of the observational studies reporting on pregnancies exposed to interferon beta-1b did not identify an association between the use of interferon beta-1b during pregnancy and an increased risk of major birth defects. <u>Animal Data</u> When BETASERON (doses ranging from 0.028 to 0.42 mg/kg/day) was administered to pregnant rhesus monkeys throughout the period of organogenesis (gestation days 20 to 70), a dose-related abortifacient effect was observed. The low-effect dose is approximately 3 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. A no-effect dose for embryo-fetal

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	developmental toxicity in rhesus monkeys was not established.
EU package insert (the December 2020 version)	**4.3 Contraindications** <No related description> **4.6 Fertility, pregnancy and lactation** <u>Pregnancy</u> A large amount of data (more than 1000 pregnancy outcomes) from interferon beta registries, national registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure or exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited. Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far. If clinically needed, the use of Betaferon may be considered during pregnancy.
German package insert (the December 2020 version)	**4.3 Gegenanzeigen** <No related description> **4.6 Fertilität, Schwangerschaft und Stillzeit** <u>Schwangerschaft</u> Weitreichende Erfahrungen (mehr als 1000 Schwangerschaftsausgänge) aus Interferon-beta-Registern, nationalen Registern und nach Markteinführung deuten nicht auf ein erhöhtes Risiko für schwerwiegende angeborene Fehlbildungen nach Exposition vor der Empfängnis oder im ersten Schwangerschaftstrimenon hin. Die Dauer der Exposition während

	des ersten Trimenons ist jedoch nicht genau bekannt, da die Daten zu einem Zeitpunkt erhoben wurden, als die Anwendung von Interferon beta während der Schwangerschaft kontraindiziert war und die Behandlung wahrscheinlich unterbrochen wurde, als eine Schwangerschaft festgestellt und/oder bestätigt wurde. Die Erfahrungen mit einer Exposition während des zweiten und dritten Schwangerschaftstrimenons sind sehr begrenzt. Basierend auf Daten aus Tierstudien (siehe Abschnitt 5.3) besteht ein potenziell erhöhtes Risiko für Spontanaborte. Das Risiko von Spontanaborten bei mit Interferon beta exponierten schwangeren Frauen kann anhand der derzeit vorliegenden Daten nicht ausreichend bewertet werden, aber die Daten weisen bisher nicht auf ein erhöhtes Risiko hin. Falls klinisch erforderlich, kann die Anwendung von Betaferon während der Schwangerschaft in Betracht gezogen werden.
French package insert (the October 2019 verseion)	**4.3 Contre-indications** <No related description> **4.6 Fertilité, grossesse et allaitement** <u>Grossesse</u> Un grand nombre de données (plus de 1 000 grossesses), issues de registres concernant l'interféron bêta, des registres nationaux et de données post-commercialisation, n'a pas mis en evidence un risque augmenté de malformations congénitales majeures après une exposition précédant la conception ou au cours du premier trimestre de grossesse. Néanmoins, la durée de l'exposition au cours du premier trimestre est incertaine car les données ont été recueillies alors que l'utilisation de l'interféron bêta était contre-indiquée pendant la grossesse, et le traitement a probablement été interrompu lorsque la grossesse a été détectée et/ou confirmée. Les données concernant l'exposition durant le deuxième et le troisième trimestre de la grossesse sont très limitées. D'après les données animales (voir rubrique 5.3), le risque

	d'avortement spontané pourrait être augmenté. Les données actuellement disponibles chez les femmes enceintes exposées à l'interféron bêta ne permettent pas d'évaluer correctement le risque d'avortement spontané, mais à ce jour, ces données ne suggèrent pas d'augmentation de ce risque. Si l'état clinique le nécessite, l'utilisation de Betaferon peut être envisagée pendant la grossesse.
Canadian package insert (the August 2021 version)	CONTRAINDICATIONS <No related description> Special Populations Pregnant women. There are no controlled clinical studies of BETASERON in pregnant women. The administration of BETASERON during confirmed pregnancy should be avoided, unless clearly needed. A European registry study collected data on 778 prospective pregnancies in women with MS who were treated with one of five interferon beta medications. The rates of aggregated adverse pregnancy outcomes were in line with reference ranges published in the literature. Data from a retrospective register-based study in Sweden and Finland have likewise not indicated an increased risk of major congenital anomalies after early pregnancy exposure. However, the duration of exposure during the first trimester was uncertain since data were collected when interferon beta use was contraindicated during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health. BETASERON was not teratogenic at doses up to 0.42 mg (13.3 MIU)/kg/day in rhesus monkeys, but demonstrated dose-related

	abortifacient activity when administered at doses ranging from 0.028 mg (0.89 MIU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 MIU)/kg/day (40 times the recommended human dose based on body surface area comparison). It is not known if animal doses can be extrapolated to human doses. Lower doses were not studied in monkeys. BETASERON given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot be evaluated based on the currently available data.
Australian package insert (the April 2021 version)	4.3 CONTRAINDICATIONS <No related description> 4.6 FERTILITY, PREGNANCY AND LACTATION Use in pregnancy – Pregnancy Category D BETAFERON was not teratogenic in rhesus monkeys at doses up to 13.3 million IU/kg/day SC, but demonstrated an abortifacient activity when administered at doses ranging from 0.89 to 24 million IU/kg/day. It is not known whether interferon beta-1b can cause foetal harm when administered to a pregnant woman or can affect human reproductive capacity. Data from pregnancy registries and post-marketing experience on the use of BETAFERON in pregnant women (exposures mostly during the first trimester) suggest that frequencies of miscarriage and congenital abnormalities were comparable with the estimated background risk in the general population. Miscarriages have been reported in subjects with MS in controlled clinical trials with incidence rates not exceeding those in the general population. Therefore, women of child-bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking interferon beta-1b, she should be informed of the potential hazards and discontinuation of therapy should be considered; the benefits and possible risks of continuing

	BETAFERON therapy are recommended to be weighed. The individual disease severity and the potential detrimental effects that could occur if medication is stopped should be discussed with the patient.

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Appendix 3

Materials describing the status of data collection of adverse reactions occurring in Japan

Interferon beta-1a (genetical recombination)

No.	Reporting year	Age	Sex	Adverse reactions (PT)	Route of administration	Outcome	Reason for use
1	2013	43	Female	Stillbirth	Intramuscular	Unknown	Relapsing-remitting multiple sclerosis
2 Note 1)	2013	31	Female	Spontaneous abortions	Intramuscular	Unknown	Relapsing-remitting multiple sclerosis

Interferon beta-1b (genetical recombination)

No.	Reporting year	Age	Sex	Adverse reactions (PT)	Route of administration	Outcome	Reason for use
1 Note 1)	2006	34	Female	Threatened labour Placenta praevia	Subcutaneous	Recovered	Relapsing-remitting multiple sclerosis

Note 1) This is a report from Drug use-results survey.

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Appendix 4

Summary of research reports

No.	Relevant literature	Summary
1	Portaccio E, et al. Interferon beta therapy and Pregnancy outcomes in patients with multiple sclerosis. InMULTIPLE SCLEROSIS 2008 (Vol. 14, pp. S174-S174).	Italian MS patients were recruited and pregnancy data of 432 patients whose pregnancy was recorded in the period of 1996 - 2007 were collected. Regarding pregnancy outcomes, 72 cases were live birth and 10 cases were non-live birth in the group exposed to IFN-beta (IFNβ) during pregnancy, 90 cases were live birth and 7 cases were non-live birth in the group exposed to IFNβ more than 1 month before pregnancy, and 155 cases were live birth and 5 cases were non-live birth in the IFNβ non-exposed group. IFNβ exposure was not significantly associated with spontaneous abortions (odds ratio 0.99, 95% CI: 0.29-3.37, p=0.98).
2	Hellwig K, et al. Interferon beta, birth weight and pregnancy in multiple sclerosis. Journal of neurology. 2009;256(5):830.	Among 220 cases of pregnancy in the database of female MS patients with a pregnancy or child delivery over the last 10 years, 17 pregnancies of women of MS (mean age 31.7 years; duration of MS 6.2 years) with exposure to INFβ during early pregnancy (INFβ exposure until gestational week 4.7 on average) were followed prospectively. As a result, 2 miscarriages were observed.
3	Hellwig K, et al. Parenthood and immunomodulation in patients with	The clinical outcomes of pregnancies fathered by MS patients under DMT (IFNβ, natalizumab, glatiramer acetate, methotrexate, etc.) were investigated. Among 46 foetuses,

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	multiple sclerosis. Journal of neurology. 2010;257(4):580-3.	6 (13%) ended in early miscarriage, 2 (5%) were premature baby, 1 (2.5%) had a spinal cord lipoma, and 3 (7.5%) had moderate hip dysplasia.
4	Uçar İL, et al. The potential teratogenic effects of interferon beta-1a and interferon beta-1b on in vitro embryonic development. Folia morphologica. 2016;75(2):257-63.	IFNβ was applied to the culture medium and after 48 hours of culture, effects of IFNβ (1000 IU/IFNβ-1a and 1000 IU/IFNβ-1b) on embryonic development were morphologically investigated. As a result, IFNβ-1a and IFNβ-1b did not have a macroscopic teratogenic effect on embryonic development. However, in respect to morphometric measurements, IFNβ-1a and IFNβ-1b caused growth retardation in embryo.