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 the Investigation Results

August 24, 2017
Pharmaceutical and Medical Devices Agency

I. Overview of Product

[Non-proprietary name] Interferon beta

[Brand name] Feron 1 million for injection, 3 million for injection, 6 million for injection

[Approval holder] Toray Industries, Inc.

[Indications] Glioblastoma, medulloblastoma, astrocytoma, malignant melanoma of skin,
Improvement of viraemia in chronic active hepatitis B patients positive for HBe antigen and DNA polymerase,
Improvement of viraemia in chronic hepatitis C,
Improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C patients falling under any of the following descriptions:
(1) Patients with high blood HCV-RNA levels
(2) Patients who did not respond to interferon monotherapy or relapsed after interferon monotherapy
Improvement of viraemia in compensated cirrhosis type C (excluding the cases with HCV serogroup 1 and high blood HCV-RNA level)

[Dosage and administration] Glioblastoma, medulloblastoma, astrocytoma
Topical administration
Should be reconstituted in an appropriate amount of the supplied reconstitution diluent. The usual adult dosage is 1 to 6 MIU per day administered intraspinally (including intratumorally). The dose may be adjusted according to the patient's age and symptoms.
Intravenous infusion
Should be reconstituted in isotonic sodium chloride solution or 5% glucose solution for injection, etc. The usual adult dosage is 1 to 6 MIU per day by intravenous infusion. The dose may be adjusted according to the patient's age and symptoms.
Malignant melanoma of skin

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Should be reconstituted in an appropriate amount of the supplied reconstitution diluent. The usual adult dosage is 400 000 to 800 000 IU per lesion once daily, administered intratumorally or into the surrounding area.

The total daily dosage is 1 to 3 MIU. The dose may be adjusted according to the size and condition of tumor as well as the patient's age and symptoms.

Improvement of viraemia in chronic active hepatitis B patients positive for HBe antigen and DNA polymerase

Intravenous injection or intravenous infusion

Should be reconstituted in isotonic sodium chloride solution or 5% glucose solution for injection, etc. The usual adult dosage is 3 MIU per dose once on the first day, once to twice daily for the next 6 days, and once daily from Week 2 onward by intravenous injection or intravenous infusion.

Improvement of viraemia in chronic hepatitis C

Intravenous injection or intravenous infusion

Should be used only after confirming that the patient tests positive for HCV-RNA.

Should be reconstituted in isotonic sodium chloride solution or 5% glucose solution for injection, etc. The usual adult dosage is 3 to 6 MIU administered consecutively once daily by intravenous injection or intravenous infusion.

Improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C patients

Intravenous injection or intravenous infusion

Should be used only after confirming that the patient tests positive for HCV-RNA.

Should be reconstituted in isotonic sodium chloride solution or 5% glucose solution for injection, etc. The usual adult dosage is 6 MIU daily for the first 4 weeks and 3 times a week thereafter by intravenous injection or intravenous infusion.

Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1)

Intravenous injection or intravenous infusion

Should be used only after confirming that the patient tests positive for HCV-RNA.

Should be reconstituted in isotonic sodium chloride solution or 5% glucose solution for injection, etc. The

usual adult dosage is 6 MIU per day initially, 3 to 6 MIU daily for the first 6 weeks and 3 MIU per day 3 times a week thereafter by intravenous injection or intravenous infusion.

[Remarks] None in particular

[Investigating office] Office of Safety II

II. Background of the investigation

1. Background up to the time of approval

Interferon beta was approved in Japan for the indications of “malignant melanoma of skin” and “glioblastoma” in April 1985, after which it was approved for the indications of “improvement of viraemia in chronic active hepatitis B patients positive for HBe antigen and DNA polymerase”, “medulloblastoma”, “astrocytoma”, “improvement of viraemia in chronic hepatitis C”, “improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1)” (compensated cirrhosis type C), and “improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C patients falling under any of the following descriptions: (1) Patients with high blood HCV-RNA levels, or (2) Patients who did not respond to interferon monotherapy or relapsed after interferon monotherapy”.

A partial change in the approved product information (partial change approval) for the indication of compensated cirrhosis type C was approved in April 2006 and reflected in the Dosage and Administration, Precautions of Dosage and Administration, and Important Precautions as follows.

[Dosage and Administration] (Excerpt)

The usual adult dosage is 6 MIU per day initially, 3 to 6 MIU daily for the first 6 weeks and 3 MIU per day 3 times a week thereafter by intravenous injection or intravenous infusion.

[Precautions of Dosage and Administration] (Excerpt)

The treatment duration should be carefully determined taking into account the clinical efficacy and severity of adverse drug reactions. The usual adult dosage is 6 MIU per day for 1 week, followed by 3 MIU daily for 5 weeks, and 3 MIU per day 3 times a week from Week 7 onward by intravenous injection or intravenous infusion.

[Important Precautions] (Excerpt)

When administering interferon beta long term, the clinical efficacy and severity of adverse drug reactions should be considered and administration should be discontinued if no efficacy is observed. Efficacy and safety are not established for administration for more than 48 weeks (total dosage of 936 MIU) regarding the improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C or for more than 34 to 36 weeks (total dosage of 399 MIU) regarding the improvement of viraemia in compensated cirrhosis type C (Refer to Clinical Studies section).

In the process of the partial change approval review for compensated cirrhosis type C, patients with high viral levels showed a low negative conversion rate of HCV-RNA at 6 months after the end of administration of interferon beta in the Japanese phase 3 study[1)]. It was assumed that extended administration of 6 MIU/day is feasible by establishing criteria for dosage reduction, discontinuation, suspension, and resumption of administration, and improvement was expected in the percentage of patients with negative conversion of HCV-RNA even in refractory patients with high viral levels.

However, the criteria for dosage reduction, discontinuation, suspension, and resumption of administration in the current Important Precautions were established with reference to data on similar drugs and no data were available regarding the efficacy and safety for administration and dosage higher than in the high dose group of the Japanese phase 3 study. Therefore, the approval was granted on the basis of the dosage and administration for the high-dose group investigated in the Japanese phase 3 study, and further post-marketing investigation was considered necessary for optimization of dosage and administration.

2. Background leading to the current investigation

Based on the findings during the partial change approval review for compensated cirrhosis type C, a post-marketing clinical study was performed with the objective of considering the efficacy and safety when total treatment duration and treatment duration for 6 MIU/day were extended, and appropriateness of the criteria for dosage reduction and discontinuation of administration.

The results of the re-examination of the indication of compensated cirrhosis type C were announced in March 2011, and none of the parts of Article 14, Paragraph (2), Item (iii) of the Pharmaceutical Affairs Law were deemed applicable. However, since enrollment of subjects in the post-marketing clinical study was difficult and took a considerable length of time, the results of the interim analysis were submitted in the re-examination, and it was decided to wait until the results of the final analysis were submitted for the examination of the efficacy and safety when the total treatment duration and the treatment duration for 6 MIU/day were extended, as well as the criteria for dosage reduction and discontinuation of administration.

Since the final results of the post-marketing clinical study were obtained in April 2015, the marketing authorization holder applied for a consultation on revision of the package insert on the basis of the study results, and PMDA considered the necessity of revising the

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1) A randomized, open-label, parallel-group comparative study was conducted for the purpose of investigating the efficacy and safety of interferon beta in patients with compensated cirrhosis type C having low viral level or other than HCV serogroup 1 (target number 150 cases). Dosage and administration were as follows.

- Low-dose group: 6 MIUs were administered daily for 1 week, followed by 3 MIUs daily for 5 weeks for a total of 42 doses (treatment duration of 6 to 7 weeks, total dosage of 147 MIU)
- Medium-dose group: 6 MIUs were administered daily for 1 week, followed by 3 MIUs daily for 5 weeks and 3 MIUs per day 3 times a week from Week 7 onward, for a total of 84 doses (treatment duration of 20 to 22 weeks, total dosage of 273 MIU)
- High-dose group: 6 MIUs were administered daily for 1 week, followed by 3 MIUs daily for 5 weeks and 3 MIUs per day 3 times a week from Week 7 onward, for a total of 126 doses (treatment duration of 34 to 36 weeks, total dosage of 399 MIUs)

package insert on the basis of the study results.

PMDA has held an Expert Discussion as part of the investigations. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the products, and in accordance with the "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

III. Summary of submitted data, etc.

1. Post-marketing clinical study (Study No. 532LCV03 < Dec. 2006 to May 2013 >)

A randomized, open-label, parallel-group comparative study was conducted in patients with compensated cirrhosis type C[2] (target number: 237 cases, 79 cases in each group) with the objective of considering the efficacy and safety when the total treatment duration and treatment duration for 6 MIU/day were extended, and appropriateness of the criteria for dosage reductions and discontinuation of administration[3].

Dosage and administration were specified as follows. Group I[4]: 6 MIU daily for 1 week, followed by 3 MIU daily for 5 weeks and 3 MIU per day 3 times a week from week 7 onward, for a total of 126 doses (treatment duration of 34 to 36 weeks, total dosage of 399 MIU); Group II: 6 MIU daily for 1 week, followed by 3 MIU daily for 5 weeks and 3 MIU per day 3 times a week from Week 7 onward, for a total of 168 doses(treatment duration of 48 to 50 weeks, total dosage of 525 MIU); Group III: 6 MIU daily for the first 6 weeks and 3 MIU per day 3 times a week from week 7 onward, for a total of 168 doses (treatment duration of 48 to 50 weeks, total dosage of 630 MIU) (Fig. 1).

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2) Key inclusion criteria: Patient with blood HCV-RNA levels <1 Meq/mL (bDNA probe method), <100 KIU/mL (Amplicor method), or <5.0 LogIU/mL (Cobas TaqMan HCV method), or compensated cirrhosis type C patient other than HCV serogroup 1, patient confirmed not to have complication of liver cancer by diagnostic imaging performed within 24 weeks prior to enrollment, patient that fulfills all conditions [1] and [2] in the most recent laboratory test measurements made within 4 weeks prior to enrollment ([1] WBC count ≥3 000/mm^3, [2] platelet count ≥70 000/mm^3), patient testing negative for HBs antigen, patient aged 20 or older at time of consent, patient who can be hospitalized for 2 weeks or more, from the starting date of administration onward (irrespective of sex)

3) When any of the following laboratory test abnormalities are observed, dosage reduction, prolongation of dosing interval, or discontinuation of administration should be considered.
[1] WBC count (<1 500/mm^3: dosage reduction or prolongation of dosing interval; <1000/mm^3: discontinuation of administration)
[2] Neutrophil count (<750/mm^3: dosage reduction or prolongation of dosing interval; <500/mm^3: discontinuation of administration)
[3] Platelet count (<50 000/mm^3: dosage reduction or prolongation of dosing interval; <25 000/mm^3: discontinuation of administration)

4) Group I has the same dosage and administration as the high-dose group in the Japanese phase 3 study that was the basis for Precautions Related to Dosage and Administration.

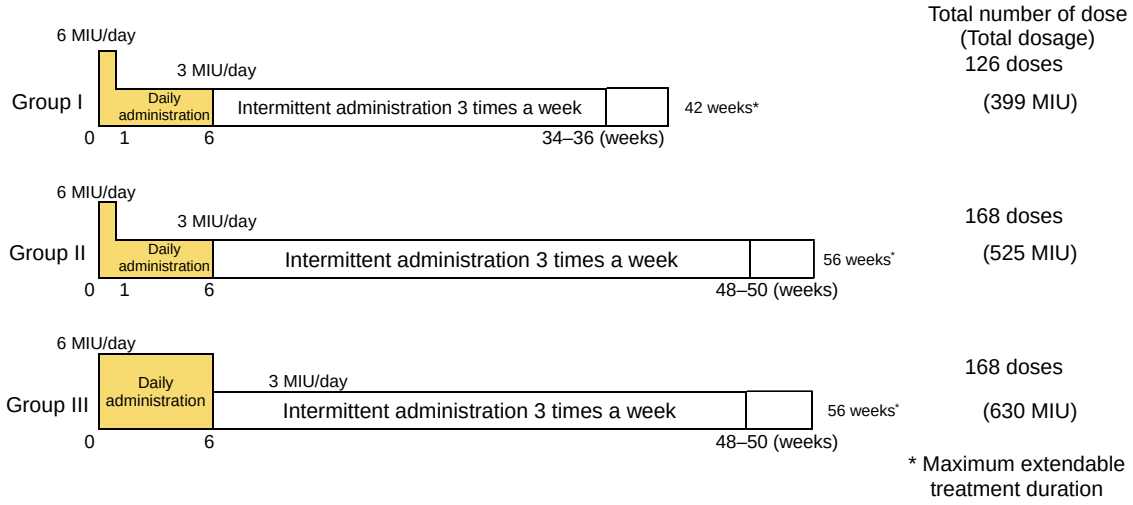

Fig. 1 Dosage and administration in each group

All 212 cases in which the drug was administered (71 cases in Group 1, 70 cases in Group II, 71 cases in Group III) were included in the safety analysis set and Full Analysis Set (FAS), and the FAS was considered the main efficacy analysis set.

In the efficacy analysis, the negative conversion rate of HCV-RNA[5)], which was the primary endpoint, is shown in Table 1. No statistically significant difference was observed in Group III compared to Group I (p-value = 1.0000, Fisher's exact test, two-tailed level of significance 10%[6)]). Comparison of Group I vs. Group II and Group II vs. Group III was not performed because the plan was to perform the test if superiority of Group III to Group I was observed (closed testing procedure). The negative conversion rate of HCV-RNA by serogroup and viral level was as shown in Table 2.

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5) Percentage of cases showing negative blood HCV-RNA 24 weeks after the end of administration when evaluated by [1] or [2]
[1] Amplicor quantitation method (I: negative (SVR); II: positive (including false positives); III: undeterminable, when it cannot be determined because of missing data)
[2] Cobas TaqMan HCV method
I. Negative (SVR): When blood HCV-RNA levels are <1.2 LogIU/mL and undetectable
II. Positive (including false positives): When blood HCV-RNA levels are <1.2 LogIU/mL but detectable, or when blood HCV-RNA levels are ≥1.2 LogIU/mL
III. Undeterminable: When it cannot be determined because of missing data.

6) In Japan, the number of patients with compensated cirrhosis type C is extremely limited, so it was difficult to secure a sufficient number of patients for the post-marketing clinical study. For this reason, the level of two-tailed significance was set at 10%.

Table 1 Negative conversion rate of HCV-RNA 24 weeks after end of administration [a]

Dose group	Negative conversion rate of HCV-RNA	Between-group difference with Group I [90% CI]
Group I	25.4 (18/71)	-
Group II	25.7 (18/70)	-
Group III	25.4 (18/71)	0.0 [- 14.4, 14.4]

Unit: % (number of cases), CI: confidence interval (two-tailed), –: N/A
a) Indeterminate cases (20 cases in Group I; 28 cases in Group II; 27 cases in Group III) were tallied as cases without negative conversion

Table 2 Negative conversion rate of HCV-RNA 24 weeks after end of administration by serogroup and viral level

HCV serogroup	HCV-RNA level	Negative conversion rate of HCV-RNA [a)]		
		Group I	Group II	Group III
Serogroup 1	<100 KIU/mL or <5.0 logIU/mL	50.0 (4/8) [b)]	55.6 (5/9) [b)]	50.0 (5/10) [b)]
Other serogroups	<100 KIU/mL or <5.0 logIU/mL	52.4 (11/21) [c)]	50.0 (8/16) [c)]	45.5 (10/22) [c)]
	≥100 KIU/mL or ≥5.0 logIU/mL	7.7 (3/39) [d)]	7.5 (3/40) [d)]	5.6 (2/36) [d)]

Unit: % (number of cases)
a) Indeterminable cases were tallied as cases without negative conversion.
b) Number of indeterminable cases was 3 in Group I, 2 in Group II, 2 in Group III respectively.
c) Number of indeterminable cases was 4 in Group I, 4 in Group II, 8 in Group III respectively.

Number of indeterminable cases was 12 in Group I, 20 in Group II, 16 in Group III respectively.

Moreover, the rate of sustained ALT normalization[7),8)], one of the secondary endpoints, was 44.8% (30/67 cases) in Group I, 34.8% (23/66 cases) in Group II, and 40.3% (27/67 cases) in Group III.

In the safety analysis, adverse events (AEs) and AEs for which a causal relationship to interferon beta could not be ruled out (adverse drug reactions [ADR]) were observed in all cases in Group I, Group II, and Group III. AE and ADRs for which the incidence was 20% or higher in any one of the dose groups are shown in Table 2.

7) The sustained ALT normalization rate established as a secondary endpoint was calculated as the percentage of cases in which the drug was effective when evaluated for “sustained ALT normalization for 24 weeks (168 days) or more when ALT normalized within 24 weeks after the end of administration” based on the following criteria set forth by the MHLW Investigative Research Team for Specific Disease “Refractory Hepatitis” Treatment Subcommittee Response Evaluation Criteria 1992.
   I. Effective: When ALT normalized within 24 weeks after the end of administration, and a normal value was sustained for 24 weeks (168 days) or more thereafter
   II. Ineffective: When it does not correspond to I or III
   III. Undeterminable: When it cannot be determined because of missing data

8) Undeterminable cases were tallied as cases with unsustained normalization (21 cases in Group I; 28 cases in Group II; 24 cases in Group III).

Table 3 Adverse events and adverse drug reactions for which the incidence was 20% or higher in any one of the dose groups

	Adverse events			Adverse drug reactions		
	Group I	Group II	Group III	Group I	Group II	Group III
No. of cases evaluated	71	70	71	71	70	71
All events	71 (100)	70 (100)	71 (100)	71 (100)	70 (100)	71 (100)
Pyrexia	65 (91.5)	69 (98.6)	65 (91.5)	65 (91.5)	69 (98.6)	65 (91.5)
Decreased neutrophil count	55 (77.5)	58 (82.9)	65 (91.5)	55 (77.5)	58 (82.9)	65 (91.5)
Decreased platelet count	63 (88.7)	63 (90.0)	61 (85.9)	62 (87.3)	63 (90.0)	61 (85.9)
Malaise	49 (69.0)	48 (68.6)	58 (81.7)	49 (69.0)	48 (68.6)	57 (80.3)
Chills	44 (62.0)	56 (80.0)	51 (71.8)	44 (62.0)	56 (80.0)	51 (71.8)
Protein urine present	43 (60.6)	47 (67.1)	52 (73.2)	42 (59.2)	47 (67.1)	51 (71.8)
Increased lymphocyte count	44 (62.0)	51 (72.9)	43 (60.6)	43 (60.6)	50 (71.4)	43 (60.6)
Decreased white blood cell (WBC) count	48 (67.6)	46 (65.7)	51 (71.8)	48 (67.6)	46 (65.7)	51 (71.8)
Headache	41 (57.7)	46 (65.7)	42 (59.2)	41 (57.7)	46 (65.7)	41 (57.7)
Decreased blood albumin	36 (50.7)	43 (61.4)	42 (59.2)	30 (42.3)	42 (60.0)	39 (54.9)
Increased monocyte count	42 (59.2)	39 (55.7)	36 (50.7)	41 (57.7)	38 (54.3)	36 (50.7)
Decreased granulocyte count	33 (46.5)	37 (52.9)	39 (54.9)	33 (46.5)	37 (52.9)	39 (54.9)
Arthralgia	25 (35.2)	35 (50.0)	37 (52.1)	23 (32.4)	31 (44.3)	37 (52.1)
Increased blood lactate dehydrogenase	18 (25.4)	26 (37.1)	32 (45.1)	15 (21.1)	21 (30.0)	25 (35.2)
Blood urine present	19 (26.8)	16 (22.9)	31 (43.7)	17 (23.9)	13 (18.6)	26 (36.6)
Increased ALT	29 (40.8)	25 (35.7)	30 (42.3)	23 (32.4)	22 (31.4)	27 (38.0)
Increased AST	29 (40.8)	27 (38.6)	29 (40.8)	24 (33.8)	24 (34.3)	25 (35.2)
Nasopharyngitis	20 (28.2)	28 (40.0)	23 (32.4)	7 (9.9)	3 (4.3)	7 (9.9)
Decreased haematocrit	21 (29.6)	24 (34.3)	25 (35.2)	19 (26.8)	20 (28.6)	24 (33.8)
Decreased appetite	22 (31.0)	23 (32.9)	24 (33.8)	22 (31.0)	22 (31.4)	24 (33.8)
Decreased haemoglobin	24 (33.8)	23 (32.9)	22 (31.0)	20 (28.2)	18 (25.7)	21 (29.6)
Decreased total protein	21 (29.6)	17 (24.3)	24 (33.8)	20 (28.2)	17 (24.3)	22 (31.0)
Decreased blood cholesterol	23 (32.4)	18 (25.7)	13 (18.3)	21 (29.6)	17 (24.3)	13 (18.3)
Decreased red blood cell count	16 (22.5)	21 (30.0)	20 (28.2)	13 (18.3)	19 (27.1)	20 (28.2)
Increased blood ALP	18 (25.4)	14 (20.0)	21 (29.6)	14 (19.7)	13 (18.6)	19 (26.8)
Glucose urine present	14 (19.7)	20 (28.6)	17 (23.9)	8 (11.3)	14 (20.0)	15 (21.1)
Increased γ-GTP	15 (21.1)	15 (21.4)	20 (28.2)	11 (15.5)	9 (12.9)	18 (25.4)
Constipation	11 (15.5)	7 (10.0)	19 (26.8)	6 (8.5)	5 (7.1)	13 (18.3)
Increased eosinophil count	11 (15.5)	15 (21.4)	11 (15.5)	10 (14.1)	15 (21.4)	11 (15.5)
Increased blood urea	15 (21.1)	14 (20.0)	15 (21.1)	8 (11.3)	11 (15.7)	13 (18.3)
Pruritus	9 (12.7)	11 (15.7)	15 (21.1)	8 (11.3)	10 (14.3)	12 (16.9)
Back pain	8 (11.3)	14 (20.0)	11 (15.5)	6 (8.5)	13 (18.6)	10 (14.1)
Diarrhoea	12 (16.9)	14 (20.0)	12 (16.9)	6 (8.5)	5 (7.1)	7 (9.9)

Number of cases with AEs or ADRs (incidence %), MedDRA/J ver.16.1

One death (cardiac failure) was observed in Group I, and a causal relationship to interferon beta was not ruled out. The incidence of serious AEs was 73.2% (52/71 cases) in Group I, 72.9% (51/70 cases) in Group II, and 81.7% (58/71 cases) in Group III. The incidence of serious adverse drug reactions was 66.2% (47/71 cases) in Group I, 68.6% (48/70 cases) in Group II, and 78.9% (56/71 cases) in Group III.

Of the criteria for dosage reduction and discontinuation of administration, the percentage of cases meeting the Dosage Reduction or Prolongation of Dosing Interval criteria, was 47.9% (34/71 cases) in Group I, 54.3% (38/70 cases) in Group II, and 59.2% (42/71 cases) in Group III, respectively, while the percentage of cases meeting the Discontinuation of Administration criteria was 8.5% (6/71 cases) in Group I, 10.0% (7/70

cases) in Group II, and 18.3% (13/71 cases) in Group III, respectively, both in light of specified values of WBC count, neutrophil count, and platelet count.

The percentages of cases with dosage reductions or prolongation of the dosing interval and the percentage of cases with discontinued administration are shown in Table 4. Among the cases in which administration was discontinued due to AEs, the main events responsible for the discontinuation, apart from decreased WBC count, decreased neutrophil count, or decreased platelet count, were 6 cases of hepatocellular carcinoma (2 cases in Group II, 4 cases in Group III); 2 cases of AST and increased ALT (1 case in Group I, 1 case in Group III); 2 cases of malaise (1 case in Group I, 1 case in Group III); and 2 cases of ascites (1 case in Group II, 1 case in Group III). Of these, 2 cases of AST and increased ALT (1 case in Group I, 1 case in Group III), 2 cases of malaise (1 case in Group 1, 1 case in Group III), and 1 case of ascites (1 case in Group II) were all determined to be adverse drug reactions.

Table 4 Percentages of cases with dosage reduction, prolongation of dosing interval, or discontinuation

	Group I	Group II	Group III
Number of cases evaluated	71	70	71
Dosage reduction or prolongation of dosing interval	37 (52.1)	38 (54.3)	57 (80.3)
Dosage reduction or prolongation of dosing interval due to AE	29 (40.8)	33 (47.1)	44 (62.0)
Dosage reduction or prolongation of dosing interval due to ADR	26 (36.6)	32 (45.7)	46 (64.8)
Dosage reduction or prolongation of dosing interval due to decreased WBC count or decreased neutrophil count [a)]	13 (18.3)	20 (28.6)	36 (50.7)
Dosage reduction or prolongation of dosing interval due to decreased platelet count [a)]	12(16.9)	19(24.3)	17(23.9)
Discontinuation of administration	17 (23.9)	29 (41.4)	22 (31.0)
Discontinuation of administration due to AE	8 (11.3)	11 (15.7)	15 (21.1)
Discontinuation of administration due to ADR	7 (9.9)	7 (10.0)	10 (14.1)
Discontinuation of administration due to decreased WBC count or decreased neutrophil count [a)]	0	0	1 (1.4)
Discontinuation of administration due to decreased platelet count [a)]	1 (1.4)	0	1 (1.4)

Number of cases with AEs or ADRs (incidence %) a) Some cases are duplicated.

IV. Summary of investigation at PMDA

1. Efficacy when total treatment duration and treatment duration for 6 MIU/day were extended

Because no statistically significant difference in the HCV-RNA negative conversion rate was observed in Group III compared to Group I in the post-marketing clinical study, PMDA considers that a clear improvement in efficacy was not demonstrated when the total treatment duration and treatment duration for 6 MIU/day were extended.

2. Safety of extending total treatment duration and treatment duration for 6 MIU/day as well as appropriateness of the criteria for dosage reduction and discontinuation of administration

In the post-marketing clinical study, no characteristic AEs were found to have occurred in Group III, and although there were cases in which dosage was reduced or dosing interval was prolonged due to decreased WBC count, decreased neutrophil count, or

decreased platelet count, there was only one case each of discontinuation due to decreased WBC count, decreased neutrophil count, or decreased platelet count in Group I and Group III. As such, PMDA considered there to have been no specific problems necessitating new measures in the existing criteria for dosage reduction or discontinuation based on decreased WBC count, decreased neutrophil count, or decreased platelet count at present, and provided there is compliance with the criteria for dosage reduction and discontinuation, there are thought to be no major problems with the safety of interferon beta.

However, because the percentage of cases with dosage reduction or prolongation of dosing interval due to AEs or ADRs and the percentage of cases with discontinued administration showed a tendency to be higher in Groups II and III compared to Group I, PMDA considers that it is possible that more patients will find it difficult to continue treatment with dosage and administration where the total treatment duration and treatment duration for 6 MIU/day are extended.

3. PMDA's conclusion based on the investigation results

In the "Precautions of Dosage and Administration" of the current package insert, the usual treatment duration for compensated cirrhosis type C was set at 6 MIU/day for 1 week, and the usual total treatment duration is not specified.

Because efficacy did not show a clear improvement in the post-marketing clinical study, and the percentage of cases with dosage reduction or the prolongation of dosing interval due to AEs or ADRs, as well as the percentage cases with discontinued administration, showed a tendency to be higher, PMDA concluded that extension of the total treatment duration and treatment duration for 6 MIU/day should not be recommended as the usual dosage and administration. Accordingly, PMDA considers that it would be appropriate to leave the usual treatment duration for 6 MIU/day as it is presently ("1 week"), in the "Precautions of Dosage and Administration". In regards to the total treatment duration, it would be appropriate to clearly specify the usual duration as "34–36 weeks (399 MIU as the total dosage)" to call attention, which is the same treatment duration as Group I in the post-marketing clinical study.

Moreover, PMDA considers it would be appropriate to provide information on the outcome of the post-marketing clinical study by including it under the Clinical Studies section of the package insert, and also to delete from the current Important Precautions the statement to the effect that "efficacy and safety of administering the drug for more than 34–36 weeks (399 MIU as total dosage) have not been established".

The above conclusion of PMDA was supported by the expert advisors in the Expert Discussion.

V. Overall Evaluation

PMDA concludes that the following revisions to the package inserts are appropriate.

END

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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.

[Draft Revision] Interferon beta

Underlines: additions; cross outs: deletions

Current	Draft Revision
< Precautions of Dosage and Administration > 6. Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1) Determine the treatment duration carefully, taking into account the clinical efficacy and severity of adverse drug reactions. The usual adult dosage is 6 MIU daily for 1 week, followed by 3 MIU daily for 5 weeks, and 3 MIU per day 3 times a week from Week 7 onward by intravenous injection or intravenous infusion.	**< Precautions of Dosage and Administration >** 6. Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1) Determine the treatment duration carefully, taking into account the clinical efficacy and severity of adverse drug reactions. The usual adult dosage is 6 MIU daily for 1 week, followed by 3 MIU daily for 5 weeks, and 3 MIU per day 3 times a week from Week 7 onward by intravenous injection or intravenous infusion. The usual treatment duration should be 34 to 36 weeks (399 MIU as total dosage). (Refer to Clinical Studies section)
[Precautions] **2. Important Precautions** 4) When administering interferon beta long term, consider the clinical efficacy and the severity of adverse drug reactions and discontinue administering the drug if no efficacy is observed. Efficacy and safety are not established for administration for more than 48 weeks for improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C (total dosage of 936 MIU) ~~or for more than 34 to 36 weeks for the improvement of viraemia in compensated hepatitis C (total dosage of 399 MIU~~) (Refer to Clinical Studies section).	**[Precautions]** **2. Important Precautions** 4) When administering interferon beta long term, consider the clinical efficacy and the severity of adverse drug reactions and discontinue administering the drug if no efficacy is observed. Efficacy and safety are not established for administration for more than 48 weeks for improvement of viraemia in concomitant use with ribavirin in chronic hepatitis C (total dosage of 936 MIU) (Refer to Clinical Studies section).
[Clinical Studies] 6. Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1) < Omitted >	**[Clinical Studies]** 6. Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1) < Omitted: As per existing > In the post-marketing clinical study, superiority of Group III to Group I was not

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demonstrated as a result of administering the following dosage and administration by intravenous injection or intravenous infusion.

Group I: 6.0×10^6 IU daily for 1 week, followed by 3.0×10^6 IU daily for the next 5 weeks, and 3.0×10^6 IU per day 3 times a week from week 7 onward, for a total of 126 doses (treatment duration of 34 to 36 weeks, total dosage of 399 MIU)

Group II: 6.0×10^6 IU daily for 1 week, followed by 3.0×10^6 IU daily for the next 5 weeks and 3.0×10^6 IU per day 3 times a week from week 7 onward, for a total of 168 doses (treatment duration of 48 to 50 weeks, total dosage of 525 MIU)

Group III: 6.0×10^6 IU daily for the first 6 weeks and 3.0×10^6 IU per day 3 times a week from week 7 onward, for a total of 168 doses (treatment duration of 48 to 50 weeks, total dosage of 630 MIU)

The HCV-RNA negative conversion rate (Amplicor method or Cobas TaqMan HCV method) and ALT sustained normalization rate 24 weeks after the end of administration in each group are as shown in the table below.

Dose group	Negative conversion rate[a)] of HCV-RNA	ALT sustained normalization rate[b)]
Group I	25.4% (18/71)	44.8% (30/67)
Group II	25.7% (18/70)	34.8% (23/66)
Group III	25.4% (18/71)	40.3% (27/67)

a) Indeterminate cases (20 cases in Group I; 28 cases in Group II; 27 cases in Group III) were tallied as cases without negative conversion.

b) Indeterminate cases (21 cases in Group I; 28 cases in Group II; 24 cases in Group III) were tallied as cases without sustained normalization.

Negative conversion rate of HCV-RNA 24 weeks after the end of administration by serogroup and HCV-RNA level (Amplicor method or Cobas TaqMan HCV method) was as follows:

HCV serogroup	HCV-RNA level	Negative conversion rate of HCV-RNA [a]		
		Group I	Group II	Group III
Serogroup 1	<100 KIU/mL or <5.0 logIU/mL	50.0 (4/8)	55.6 (5/9)	50.0 (5/10)
Other serogroups	<100 KIU/mL or <5.0 logIU/mL	52.4 (11/21)	50.0 (8/16)	45.5 (10/22)
	≥100 KIU/mL or ≥5.0 logIU/mL	7.7（3/39）	7.5（3/40）	5.6（2/36）

a) Indeterminable cases (19 cases in Group I; 26 cases in Group II; 26 cases in Group III) were tallied as cases without negative conversion

Percentages of cases with dosage reduction or prolongation of dosing interval, and with discontinuation of administration were as follows:

Percentage of cases with:	Group I	Group II	Group III
Dosage reduction or prolongation of dosing interval	52.1% (37/71)	54.3% (38/70)	80.3% (57/71)
Dosage reduction or prolongation of dosing interval due to adverse drug reactions	36.6% (26/71)	45.7% (32/70)	64.8% (46/71)
Discontinuation of administration	23.9% (17/71)	41.4% (29/70)	31.0% (22/71)
Discontinuation of administration due to adverse drug reductions	9.9% (7/71)	10.0% (7/70)	14.1% (10/71)

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