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Report on the Investigation Results

June 23, 2016

Pharmaceuticals and Medical Devices Agency

I. Overview of Product

[Non-proprietary name]	Fingolimod hydrochloride
[Brand name]	(a) Imusera Capsules 0.5 mg
	(b) Gilenya Capsules 0.5 mg
[Approval holder]	(a) Mitsubishi Tanabe Pharma Corporation
	(b) Novartis Pharma K.K.
[Indications]	the prevention of relapse and delaying the accumulation of physical disability in multiple sclerosis
[Dosage and administration]	The recommended adult dosage is 0.5 mg of fingolimod hydrochloride orally administered once daily.
[Investigating office]	Office of Safety II

II. Background of the investigation

1. Status in Japan

Fingolimod hydrochloride was designated as an orphan drug with the scheduled indication for “the prevention of relapse and delaying progression of multiple sclerosis” on September 13, 2007. It was approved as a drug with a new active ingredient with indications for “the prevention of relapse and delaying the accumulation of physical disability in multiple sclerosis” on September 26, 2011.

Multiple sclerosis (MS) is an autoimmune disease with multiple inflammatory demyelinated lesions in the central nervous system such as the cerebrum or spinal cord. The disease type of MS is categorized based on the clinical course. Relapsing-remitting MS (RRMS) refers to when acute exacerbation (relapse) and remission occurs repeatedly. Primary progressive MS (PPMS) refers to when the disease progresses from onset of symptoms without any clear relapse. RRMS may transition into a different disease type, secondary progressive MS

(SPMS), which refers to when conditions progress while suffering from RRMS without any clear relapse. (Definitions are based on the 2010 Multiple Sclerosis Guidelines written by the authors of “Multiple Sclerosis Treatment Guidelines”, Igaku-Shoin 2010). In addition, RRMS and SPMS with confirmed relapse is referred to as relapsing MS.

In Japan, the manufacturing authorization application for fingolimod hydrochloride was evaluated in December 2011 using the results of domestic Phase II clinical trials [Study D1201] and overseas Phase III clinical trials [Study D2201] conducted among relapsing MS patients and the overseas Phase III clinical trials [Study D2301 and Study D2302] conducted among RRMS patients as the main clinical study results. The efficacy demonstrated in each trial is as follows.

In the domestic Study D1201 conducted among relapsing MS patients, fingolimod hydrochloride group showed superiority compared to the placebo group in terms of the primary endpoint: the percentage of patients in whom Gadolinium-detected lesions were not confirmed during MRI exams at 3 months and 6 months. In addition, in overseas Phase III clinical trials conducted among RRMS patients, significant decrease in annual relapse rate at 24 months and 12 months was confirmed among fingolimod hydrochloride group compared to the placebo group and the interferon beta-1a group, and efficacy in suppressing progression of physical disabilities, a secondary endpoint, was demonstrated compared to the placebo group. Furthermore, overseas guidelines mention that efficacy in preventing relapse among SPMS patients with confirmed relapse can be anticipated if the drug demonstrates efficacy in preventing relapse in RRMS (European Medicine Agency, *Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis,* 2015). Following an investigation result based on the available evidence, the Pharmaceuticals and Medical Devices Agency (PMDA) concluded that fingolimod hydrochloride is anticipated to be efficacious for SPMS with relapse since it has demonstrated efficacy for RRMS. On the other hand, given that efficacy and safety for PPMS was being investigated in overseas clinical trials at the time of approval and was not clarified in any of the domestic and overseas clinical trials, it was concluded that a cautionary note, “The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has yet to be established.”, should be included in the “Precautions for Indications” section.

2. Status in other countries

Since fingolimod hydrochloride was first approved overseas in Russia in August 2010 with indications for MS, it has been approved and marketed in 84 countries and regions including the US and Europe as of March 2016.

In the US, fingolimod hydrochloride was approved with indications for “GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability” in September 2010. In the EU, it was approved with the following indications in March 2011. It is not indicated for PPMS in either region.

Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:
- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy.

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Because efficacy was not demonstrated as a result of the overseas Phase III clinical trials [Study D2306] with the aim to expand indications to include PPMS (refer to the section “III. Summary of materials submitted by the marketing authorization holder of the product), the marketing authorization holder issued a press release including a flash report on results of this particular study in December 2014.

3. Events that led to recent investigations

Based on the clinical trial report for the overseas Study D2306 completed in July 2015 which indicated that fingolimod hydrochloride did not demonstrate efficacy for PPMS, the marketing authorization holder submitted a consultation for revision of the package insert to PMDA on January 19, 2016 to include the cautionary note “The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has yet to be established.” in the “Precautions for Indications” section. PMDA began its consideration based on this request.

PMDA investigated the efficacy and safety of fingolimod hydrochloride based on the overseas Study D2306, and deliberated on the necessity of revising the package insert.

Furthermore, PMDA convened an expert discussion for the investigation and the expert panel for this discussion was appointed based on offers, etc., from experts for this study drug and in accordance with regulations defined in “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 materials submitted by the marketing authorization holder of the product

Overseas Phase III trial (Study D2306 <July 2008 to December 2014>)

In order to deliberate the efficacy and safety of fingolimod, placebo-controlled, randomized, double-blinded, parallel-group comparative trials among foreign PPMS patients (target number of subjects: 940 subjects; 470 subjects in each arm) were conducted.

At the time of trial initiation, the dosage was set as placebo or fingolimod 1.25 mg orally administered once daily. However, based on the overseas Phase III trials among RRMS patients, no difference in efficacy was demonstrated between fingolimod 0.5 mg per day and fingolimod 1.25 mg per day, and safety of 0.5 mg per day was superior. Therefore, the dosage of fingolimod was switched from 1.25 mg per day to 0.5 mg per day while this trial was being conducted[1)]. Treatment duration was designed to be until completion of administration in the last subject for 36 months or maximum 5 years, and the follow-up period after completion of administration was designed to be 12 weeks.

All 970 randomized subjects (487 subjects in the placebo group, 336 subjects in fingolimod 0.5 mg/day group, and 147 subjects who switched fingolimod from 1.25 mg/day to 0.5 mg/day group [hereinafter referred to as “fingolimod 1.25/0.5 mg/day group], hereinafter displayed in the same order) is considered the Full Analysis Set (FAS), as well as the safety analysis set and the efficacy analysis set. 354 subjects discontinued treatment during the trial (170, 116, and 68 subjects respectively). The main reason for discontinuation was

[1)] Subjects who were already administered fingolimod 1.25 mg/day were switched to 0.5 mg/day while maintaining the blind. Subjects who were administered the placebo were continuously administered placebo. Subjects who enlisted after the switch over was implemented were administered either fingolimod 0.5 mg/day or placebo.

insufficient efficacy (64, 23, and 11 subjects respectively), withdrawal of consent (46, 32, and 12 subjects respectively) and adverse events (29, 28, and 25 subjects respectively).

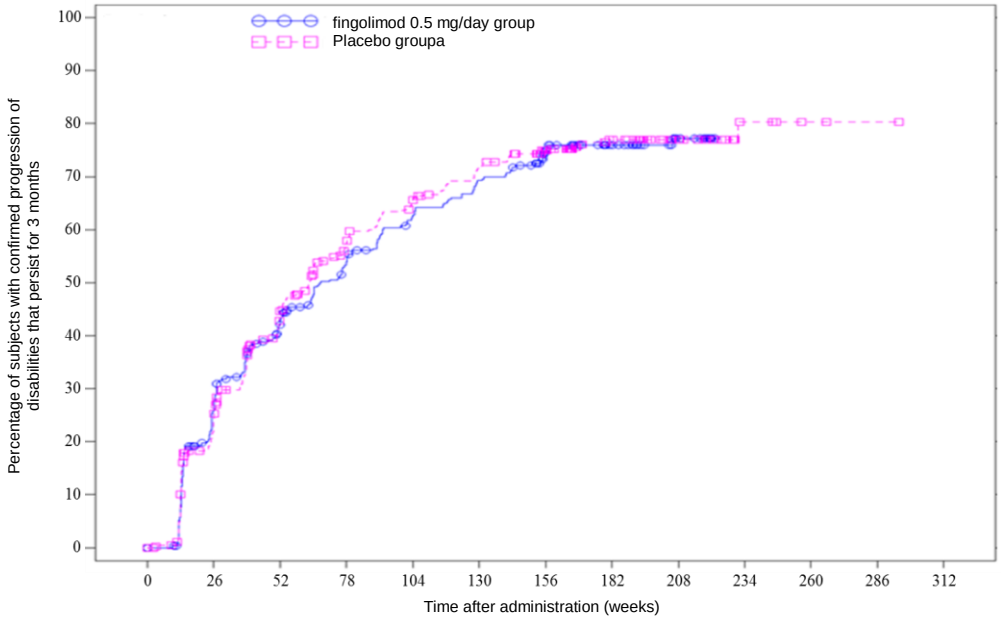
Table 1 and Figure 1 illustrates the incidence of progression of disabilities which persist for 3 months or more[2)] and the Kaplan-Meier curve based on the composite endpoint utilizing the primary endpoints Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (evaluation index for upper extremity function), and Timed 25-foot Walk Test (evaluation index for lower extremity function). fingolimod 0.5 mg/day group did not demonstrate statistically significant suppression compared to the placebo group (p=0.689, log-rank test).

Table 1 Incidence of progression of disabilities that persist for 3 months or more based on the composite endpoint utilizing EDSS, 9-Hole Peg Test, and Timed 25-foot Walk Test (FAS)

	Number of evaluated subjects	Incidence of progression of disabilities that persist for 3 months or more[a)]	Comparison to placebo		
			Hazard ratio [95% confidence interval] [b)]	p-value [b)]	p-value [c)]
Placebo group	487	80.3 [73.31, 87.25]	0.95 [0.80, 1.12]	0.544	0.689
fingolimod 0.5 mg/day	336	77.2 [71.87, 82.51]			

Incidence (%) [95% confidence interval]
a) Estimated values based on Kaplan-Meier method
b) Based on Cox regression model adjusted by treatment group, region, age, baseline EDSS, baseline 9-Hole Peg Test, and baseline Timed 25-foot Walk Test
c) log-rank test

[2)] Progression of disabilities that persist for 3 months or more was defined as conditions that apply to one of the following:
- Increase in baseline EDSS score (1-point increase among subjects with baseline EDSS score 3.5 – 5.0, 0.5-point increase among subjects with baseline EDSS score 5.5 – 6.0) persists for 3 months or more
- 20% or more increase from baseline 9-Hole Peg Test score persists for 3 months or more
- 20% or more increase from baseline Timed 25-foot Walk Test score persists for 3 months or more



Numbers At Risk

Placebo group	487	359	248	175	139	109	80	48	28	5	2	1	0
0.5 mg/day fingolimod hydrochloride group	336	239	177	134	105	86	57	33	14	0	0	0	0

Figure 1 Kaplan-Meier Curve for percentage of subjects with confirmed progression of disabilities that persist for 3 months or more based on the composite endpoint utilizing EDSS, 9-Hole Peg Test, and Timed 25-foot Walk Test

Adverse events (including abnormal laboratory test values) were observed in 95.1% of subjects in the placebo group (463/487 subjects), 96.4% in fingolimod 0.5 mg/day group (324/336 subjects), and 98.0% in fingolimod 1.25/0.5 mg/day group (144/147 subjects). Serious adverse events were observed in 24.0% of the placebo group (117/487 subjects), 25.0% of fingolimod 0.5 mg/day group (84/336 subjects), and 25.9% of fingolimod 1.25/0.5 mg/day group (34/147 subjects). The major adverse events are as described in Table 2. There were 2 fatal cases in the placebo group (1 case due to pulmonary embolism and 1 case due to convulsions), 1 fatal case in fingolimod 0.5 mg/day group (due to lung cancer with distant metastasis), and 2 fatal cases in fingolimod 1.25/0.5 mg/day group (1 case due to multiple sclerosis/respiratory tract infection and 1 case due to pneumonia aspiration). The causal relationship with the trial drug and the fatal case due to lung cancer with distant metastasis in fingolimod 0.5 mg/day group and the fatal case due to pneumonia aspiration in fingolimod 1.25/0.5 mg/day group could not be ruled out.

Table 2 Serious adverse events observed during overseas Phase III clinical trials

	Placebo group	0.5 mg/day fingolimod hydrochloride group	1.25/0.5 mg/day fingolimod hydrochloride group
Number of evaluated subjects	487	336	147

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	Placebo group	0.5 mg/day fingolimod hydrochloride group	1.25/0.5 mg/day fingolimod hydrochloride group
Serious adverse events	117 (24.0)	84 (25.0)	38 (25.9)
Major adverse events			
Basal cell carcinoma	9 (1.8)	11 (3.3)	1 (0.7)
Urinary tract infection	12 (2.5)	8 (2.4)	2 (1.4)
Squamous cell carcinoma of skin	1 (0.2)	6 (1.8)	0
Pneumonia	2 (0.4)	4 (1.2)	2 (1.4)
Macular oedema	4 (0.8)	4 (1.2)	1 (0.7)
Peripheral venous disease	2 (0.4)	4 (1.2)	0
Multiple sclerosis	5 (1.0)	3 (0.9)	2 (1.4)
Influenza	0	3 (0.9)	0
Bradycardia	0	2 (0.6)	2 (1.4)
Herpes zoster	1 (0.2)	2 (0.6)	1 (0.7)
Nephrolithiasis	1 (0.2)	2 (0.6)	1 (0.7)
Gastroenteritis	1 (0.2)	2 (0.6)	0
Constipation	1 (0.2)	2 (0.6)	0
Urinary retention	0	2 (0.6)	0
Dyspnoea	0	2 (0.6)	0
Fall	3 (0.6)	1 (0.3)	3 (2.0)
Breast cancer	0	1 (0.3)	2 (1.4)
Femur fracture	3 (0.6)	1 (0.3)	1 (0.7)
Multiple sclerosis relapse	5 (1.0)	1 (0.3)	0
Cholelithiasis	3 (0.6)	1 (0.3)	0
Acute renal failure	2 (0.4)	1 (0.3)	0
Arthralgia	2 (0.4)	1 (0.3)	0
Benign prostatic hyperplasia	2 (0.4)	1 (0.3)	0
Dehydration	2 (0.4)	1 (0.3)	0
Uhthoff's phenomenon	0	0	2 (1.4)
Appendicitis	2 (0.4)	0	1 (0.7)
Urosepsis	2 (0.4)	0	1 (0.7)
Humerus fracture	2 (0.4)	0	1 (0.7)
Joint dislocation	2 (0.4)	0	1 (0.7)
Inguinal hernia	2 (0.4)	0	1 (0.7)
Pyelonephritis	3 (0.6)	0	0
Diverticulitis	2 (0.4)	0	0
H1N1 influenza	2 (0.4)	0	0
Cerebrovascular accident	2 (0.4)	0	0
Syncope	2 (0.4)	0	0
Mobility decreased	2 (0.4)	0	0
Muscular weakness	2 (0.4)	0	0
Rhabdomyolysis	2 (0.4)	0	0
Alanine aminotransferase increased	2 (0.4)	0	0
Aspartate aminotransferase increased	2 (0.4)	0	0
Depression	2 (0.4)	0	0

Number of subjects (Incidence [%])

The causal relationship between the trial drug and the adverse events (including abnormal laboratory test values) could not be ruled out for 43.1% of cases in the placebo group (210/487 subjects), 61.9% in fingolimod 0.5 mg/day group (208/336 subjects), and 74.1% in

fingolimod 1.25/0.5 mg/day group (109/147 subjects). The major adverse events were alanine aminotransferase increased (6, 36, and 15 subjects respectively), nasopharyngitis (36, 28, and 12 subjects respectively), gamma-glutamyltransferase increased (1, 23, and 16 subjects respectively), lymphopenia (0, 19, and 12 subjects respectively), headache (23, 18, and 7 subjects respectively), hypertension (7, 16, and 12 subjects respectively), and urinary tract infection (16, 7, and 9 subjects respectively).

The percentage of subjects in whom clinically significant abnormalities in terms of vital signs (pulse rate and blood pressure) as well as electrocardiograms were confirmed during monitoring of initial administration[3)] are as outlined in Table 3.

Table 3 Percentage of subjects in whom clinically significant abnormalities were confirmed during monitoring of initial administration in overseas Phase III clinical trials

		Placebo group	Group administered fingolimod 0.5 mg	Group administered fingolimod 1.25/0.5 mg of ay
Minimum pulse rate (seated position)	Less than 45 bpm	1/487 (0.2)	1/336 (0.3)	6/147 (4.1)
Systolic blood pressure	90 mmHg or lower	18/487 (3.7)	8/336 (2.4)	8/147 (5.4)
Diastolic blood pressure	50 mmHg or lower	8/487 (1.6)	8/336 (2.4)	7/147 (4.8)
Electrocardiogram	Abnormal findings	57/478 (11.9)	86/325 (26.5)	42/143 (29.4)
	Main abnormal findings			
	Atrioventricular block first degree	11/478 (2.3)	23/325 (7.1)	14/143 (9.8)
	Sinus bradycardia	4/478 (0.8)	17/325 (5.2)	17/143 (11.9)

Number of relevant subjects/Number of evaluated subjects (Percentage [%])

Based on the above results, the marketing authorization holder explained that there was no major concern with safety even though efficacy of 0.5 mg/day fingolimod hydrochloride was not demonstrated among foreign PPMS patients.

IV. Summary of investigation by PMDA

1. Efficacy and indication for PPMS patients

In the overseas Study D2306 conducted among PPMS patients, fingolimod hydrochloride did not demonstrate superiority compared to placebo in terms of incidence of progression of disabilities that persist for 3 months or more based on the composite endpoint utilizing the

[3)] It is clear that heart rate decreases temporarily after initial administration of fingolimod hydrochloride; therefore, when initiating administration and when administration is resumed after discontinuing administration of the trial drug, blood pressure, pulse rate, and electrocardiograms are measured and blood pressure and pulse rate are monitored every hour after that. Subjects who fulfilled all criteria for hospital discharge in terms of blood pressure, pulse rate and electrocardiogram measurements 6 hours after administration were allowed to go home.

primary endpoints EDSS, 9-Hole Peg Test, and Timed 25-foot Walk Test.

Treatment goals for MS do not differ depending on disease type and aim at preventing relapse and delaying the accumulation of physical disabilities in multiple sclerosis. Taking this into consideration, the indications for MS treatment do not indicate the disease type of MS such as RRMS and SPMS but are based on the confirmed efficacy endpoints such as preventing relapse, suppressing progression of physical disabilities, etc.

Although efficacy of fingolimod hydrochloride among PPMS patients was not demonstrated in this particular overseas Study D2306, conclusions that it is ineffective for PPMS patients cannot be made based on the fact that efficacy was not shown in 1 clinical trial conducted overseas. The cautionary note “The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has yet to be established.” was included in the “Precautions for Indications” section when fingolimod hydrochloride was approved for the indications “prevention of relapse and delaying the accumulation of physical disability in multiple sclerosis ”; therefore, it is not necessary to exclude PPMS from the indications of fingolimod hydrochloride at the present time based on the overseas study results for D2306.

2. Decisions of PMDA based on investigative results

While PMDA does not think it is necessary to exclude PPMS from the indications of fingolimod hydrochloride, it is considered appropriate to include a cautionary statement in the “Precautions for Indications” section about the fact that efficacy was not confirmed among PPMS patients in the overseas Study D2306 so that healthcare professionals will carefully deliberate the benefits of treatment with fingolimod hydrochloride while taking the disease type of MS into consideration before prescription. In addition, PMDA concludes that it would be appropriate to include a summary of the results of the overseas Study D2306 in the “Other Precautions” section since efficacy not being demonstrated in the overseas Study D2306 conducted among PPMS patients is considered important information that should be disseminated in the medical field.

PMDA discussed the appropriateness of its opinion in the Expert Discussion.

On the efficacy of fingolimod for PPMS, two opinions were expressed by expert advisors. First, since the primary endpoint of overseas Study D2306 was to evaluate the motor activity alone, the efficacy of fingolimod on psychiatric symptoms or cognitive function could not be

ruled out from the study. Second, considering the nature of PPMS to progress over a long period of time, administration over a longer period could still demonstrate the efficacy for PPMS despite the fact that the overseas Study D2306, which administered fingolimod for 36 months, did not show this efficacy. The conclusion of PMDA that request for alert to the report that did not show the efficacy for PPMS included in the package insert as well as provision of the trial results are necessary was supported in the discussion.

On the other hand, an expert advisor stated that if the efficacy data in Japanese PPMS patients could be available from any post-marketing surveillance, it should be evaluated for the efficacy of fingolimod in Japanese PPMS patients.

PMDA asked the marketing authorization holder to explain the efficacy of fingolimod in the Japanese PPMS patients from the post-marketing surveillance.

The marketing authorization holder explained as follows:

Data was compiled by disease type[4], and identified 34 PPMS patients of the 1 899 patients for safety analysis (1.79%) as well as of the 1 895 patients for efficacy analysis (1.79%). The efficacy endpoints were defined for EDSS score, efficacy assessment by the physician, and clinical relapse. Relapse is not a condition observed for PPMS. Therefore. EDSS score and efficacy assessment by the physician were evaluated. As a result, the EDSS score (mean ± Standard Deviation [SD] [number of subjects assessed]) was 4.74 ± 2.35 (17 subjects) at the start of administration, 4.59 ± 2.32 (11 subjects) after 24 months of administration, and 5.00 ± 2.22 (17 subjects) at the final assessment (in the case of patient withdrawals, EDSS score was used at the discontinuation of surveillance). Change from the start of administration[5] (mean ± SD [number of subjects assessed]) was 0.41 ± 1.36 (11 subjects) after 24 months of administration and 0.26 ± 1.09 (17 subjects) at the final assessment. In the efficacy assessment by the physician (at the final assessment) in the 34 PPMS subjects, “effective” in 18 subjects (52.9%), “not effective” in 7 subjects (20.6%), and “unevaluable” in 9 subjects (26.5%).

PMDA considers as follows:

Based on the results from port-marketing surveillance described above, it should be difficult to draw a definitive conclusion on the efficacy of fingolimod in Japanese PPMS patients. On the other hand, it would be difficult to conduct clinical trials with Japanese PPMS patients alone when considering the number of Japanese MS patients who hold a

4) Unfixed cases are included in the compilation.
5) Expressed by the mean (EDSS value at each assessment point – Baseline [at the start] EDSS value) for subjects evaluated

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Certificate of Recipients of Specified Diseases Treatment reported as 19 389 in FY 2014 as well as a reported percentage, approximately 10%, of PPMS patients in 2.3 million patients diagnosed as MS worldwide. While the ongoing port-marketing surveillance or future studies will continue to accumulate data on the efficacy of fingolimod for PPMS, the current situation where fingolimod is not recommended for PPMS patients will not alter, as indicated by the description in the package insert that "The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has not yet been established." since the time of approval as precautionary statement. Therefore, clinical practices should select appropriate treatments considering the situation of individual patients.

V. Overall evaluation

PMDA concludes that that revision of the package insert was necessary with regard to descriptions on efficacy for PPMS related to fingolimod.

Underlined parts are revised

Before revision	Proposed revision
<Precautions concerning Indications> The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has not yet been established.	<Precautions concerning Indications> The efficacy and safety of fingolimod hydrochloride for progressive multiple sclerosis has not yet been established. <u>Fingolimod did not slow progression of physical disability in an overseas placebo-controlled study in patients with primary progressive multiple sclerosis.</u>
10. Other Precautions No related descriptions.	10. Other Precautions <u>In an overseas placebo-controlled, randomized, double-blind, parallel group comparison study in patients with primary progressive multiple sclerosis, patients were orally administered either fingolimod 0.5 mg or placebo once daily for 36 months (maximum 5 years). No statistically significant difference was noted in time to progression of disability persisting for 3 months, as determined by the composite endpoint based on EDSS (expanded disability</u>

	status scale), 9-Hole Peg Test (performance index of upper extremity function), and Timed 25-foot Walk Test (performance index of lower extremity function) in the 0.5 mg group compared with the placebo group (hazard ratio: 0.95, 95% confidence interval 0.80 to 1.12). [1)] [1)] Lublin, F., et al.: Lancet 2016; 387: 1075-1084