Pharmaceuticals and Medical Devices Safety Information

No. 335 August 2016

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Pharmaceuticals and Medical Devices Safety Information

No. 335 August 2016

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

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1	**Precautions Relating to the Teratogenicity of Mycophenolate Mofetil Preparations**		In Japan, a case of malformation (microtia) due to mycophenolate mofetil was reported to PMDA in February 2014, and a total of 3 cases of exposure of pregnant women to mycophenolate mofetil have been reported as of February 1, 2016, including 1 case each of spontaneous abortion and fetal death, and therefore the “Precautions” section was revised on March 23, 2016 (and corrected on March 29, 2016). As the recently added indication lupus nephritis has the characteristic of occurring frequently in women in their 20s to 40s, it is foreseen that administration of mycophenolate mofetil to women of reproductive potential will increase, and therefore we repeat below the precautions relating to the teratogenicity of mycophenolate mofetil.	4
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Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
Alb	Albumin
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BP	Blood pressure
BUN	Blood urea nitrogen
CHDF	Continuous hemodiafiltration
Cre	Creatinine
CT	Computed tomography
eGFR	Estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
IUD	Intrauterine device
MAH	Manufacturing authorization holder
Plt	Platelets
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
D-bil	Direct bilirubin
T-bil	Total bilirubin
TP	Total protein
UA	Uric acid
WBC	White blood cell count

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Precautions Relating to the Teratogenicity of Mycophenolate Mofetil Preparations

Active ingredient	Mycophenolate Mofetil
Brand name (name of company)	Cellcept Capsules 250, Powder for Suspension 31.8% (Chugai Pharmaceutical Co., Ltd.), etc.
Therapeutic category	Immunosuppressants
Indications	○ Treatment of refractory organ rejection in in patients receiving renal transplants (for patients diagnosed with refractory organ rejection for whom conventional therapy is ineffective or inappropriate due to adverse reactions). ○ Prophylaxis against organ rejection of renal transplants, cardiac transplants, hepatic transplants, lung transplants, and pancreas transplants ○ Lupus nephritis

1. Introduction

Since the time of approval in 1999, because of teratogenicity, the package insert of mycophenolate mofetil has advised caution: the drug is absolutely contraindicated in pregnant women or women suspected of being pregnant, and is relatively contraindicated in women of reproductive potential; it is advised in the "Important precautions" section that women of reproductive potential must undergo pregnancy testing, and treatment can only be initiated after confirming negative test results, and that prior to initiation through to 6 weeks after stopping treatment with this drug, patients must utilize contraception methods; and it is advised in the "Use in pregnant, parturient and nursing women" section that this drug has demonstrated teratogenic effects in humans. In Japan, nevertheless, a case of malformation (microtia) was reported to Pharmaceuticals and Medical Devices Agency (PMDA) in February 2014, and a total of 3 cases of exposure of pregnant women to mycophenolate mofetil have been reported as of February 1, 2016, including 1 case each of spontaneous abortion and fetal death, and therefore the “Precautions” section was revised on March 23, 2016 (and corrected on March 29, 2016).

As the recently added indication lupus nephritis has the characteristic of occurring frequently in women in their 20s to 40s, it is foreseen that administration of mycophenolate mofetil to women of reproductive potential will increase, and therefore we repeat below the precautions relating to the teratogenicity of mycophenolate mofetil.

2. Precautions relating to teratogenicity

(1) Explanation to patients

As mycophenolate mofetil is teratogenic, it is necessary to continue to contraindicate its use in pregnant women or women suspected of being pregnant and avoid causing exposure to mycophenolate mofetil during pregnancy. In women of reproductive potential, it is important to ensure that patients utilize reliable contraception methods prior to initiation through to 6 weeks after stopping treatment with this drug, and also to check periodically that the patient is not pregnant via methods including consultations and pregnancy tests, in order to avoid causing

exposure to mycophenolate mofetil during pregnancy. When prescribing mycophenolate mofetil to a woman of reproductive potential, explain the following points to the patient and ensure that they are understood.

- This drug has been reported to cause teratogenicity.
- Pregnancy tests must be conducted prior to initiating treatment with this drug and test results must be negative.
- Contraception must be utilized before, during and for 6 weeks after stopping treatment with this drug.
- Patients should be periodically checked by consultations and repeated pregnancy tests, etc. to ensure that no pregnancy occurs during the administration of this drug. If pregnancy is suspected, the patient should immediately contact the doctor in charge.

(2) Regular checks that the patient is not pregnant

Ministry of Health, Labour and Welfare has alerted healthcare providers to check for a negative pregnancy test before starting treatment of mycophenolate mofetil, but to ensure that exposure of pregnant women to mycophenolate mofetil is avoided, it is also important to confirm periodically during administration of mycophenolate mofetil that the patient is not pregnant. Please check periodically that the patient is not pregnant through consultations to check information such as the use of contraception, menstrual cycle, the time of the last menstrual period, and the patient's own use of pregnancy tests (see Table 1), and also by performing pregnancy tests (serum or urine human Chorionic Gonadotropin measurement) as necessary. Over-the-counter pregnancy test medication can also be used.

Table 1. Points relating to pregnancy to check at consultations

[Female patients before taking mycophenolate mofetil]

- Medical history: whether bilateral tubal ligation, hysterectomy, or bilateral oophorectomy has been performed
- Menstruation: Time of menarche/menopause, time of last menstrual period, whether or not menstrual periods are regular, and how long menstrual periods continue
- Pregnancy: whether the patient is having sexual intercourse, whether the patient is pregnant (and if so, the outcome), whether the patient can become pregnant during this menstrual cycle, whether the patient wishes to become pregnant or have children, and the patient's own use of pregnancy tests
- Contraception: the patient's level of understanding about the need for contraception, the use of contraception, and the contraception method being used

[Female patients taking mycophenolate mofetil]

- Time of last menstrual period
- Whether or not menstrual periods are regular, and how long menstrual periods continue
- Whether the patient can become pregnant during this menstrual cycle
- The patient's own use of pregnancy tests

(3) Ensuring thorough use of contraception

It is necessary to avoid pregnancy during the administration of mycophenolate mofetil by ensuring that patients utilize reliable contraception methods prior to initiation through to 6 weeks after stopping treatment with this drug. Please provide guidance to the patient so that she can carry out reliable contraception using multiple contraception methods, taking into account the characteristics, including failure rates, of contraception methods such as condoms, intrauterine devices (IUDs), and oral contraceptive drugs (the pill) (see Table 2).

Table 2. Failure (pregnancy) rate or continuation rate for contraception methods after 1 year of use

Contraception method	Ideal use* (%)	Typical use** (%)	Continuation rate for 1 year (%)
Oral contraceptive drugs (the pill)	0.3	9	67
Male condoms	2	18	43
Female condoms	5	21	41
Spermicidal agents	18	28	42
Pessaries	6	12	57
Intrauterine devices (copper IUDs)	0.6	0.8	78
Intrauterine devices (luteinizing hormone IUDs)	0.2	0.2	80
Female contraceptive surgery	0.5	0.5	100
Male contraceptive surgery	0.1	0.15	100
No contraception	85	85	

* Ideal use: If the chosen contraception method is continued correctly

** Typical use: If the contraception method is used in a typical way, including situations such as patients forgetting to take medication

<Source> *Contraception*. 2011, 83(5): 397–404. (adapted)

3. Occurrences of malformations

An investigation by the manufacturing authorization holder (MAH) (Chugai Pharmaceutical Co., Ltd.) of collected cases of congenital abnormality in Japan and overseas revealed the following malformations: ear malformations (external auditory canal atresia, microtia, etc.), eye malformations (coloboma, microphthalmos, etc.), facial malformations (hypertelorism of the orbits, micrognathia, etc.), finger malformations (syndactyly, polydactyly, brachydactyly, etc.), cardiac malformations (atrial septal defect, ventricular septal defect, etc.), esophageal malformations (esophageal atresia, etc.), and nervous system malformations (spina bifida, etc.).

In Europe, of the 57 pregnant women who were exposed to mycophenolate mofetil (22 patients received organ transplantations, 23 patients had systemic lupus erythematosus, and 12 patients had other autoimmune disorders) identified by the European Teratology Information Services from January 1998 to June 2011, the outcomes of the pregnancies were 16 spontaneous abortions, 12 elective terminations of pregnancy (including 2 late terminations due to lethal malformations), and 29 live births. Of the 29 live born infants, 6 infants had malformations, bringing the number of pregnancies having malformations to 8 (including the above mentioned 2 late terminations) (*Am J Med Genet A* 2012, 158A: 588-596). In the US, of the 97 pregnancies with exposure to mycophenolate mofetil (including 1 pregnancy with twins) reported to the National Transplantation Pregnancy Registry, 48 pregnancies (49%) resulted in spontaneous abortions, 48 resulted in live births, and of the 48 live born infants, 11 infants (23%) had malformations (*Clin Transpl.* 2009, 103-122).

The risks of this teratogenicity and abortion were added to the “Use in Pregnant, Parturient and Nursing Women” section of the package insert (see 4. Revision of Precautions (underlined parts are revised)).

4. Revision of Precautions (underlined parts are revised)

The revision of the Precautions section on March 23, 2016 (corrected on March 29, 2016), were as follows.

In the Warning section, the following text should be added:

This drug has demonstrated teratogenic effects in humans. Women of reproductive potential must undergo pregnancy testing before administration of this drug, and treatment can only be initiated after confirming negative test results. In addition, prior to initiating treatment up until 6 weeks after stopping treatment with this drug, patients must utilize reliable contraception methods and also be periodically checked by consultations and repeated pregnancy tests, etc. to ensure that no pregnancy occurs.

In the Relative Contraindications section, the following texts should be deleted:

Women of reproductive potential

In the Important Precautions section regarding teratogenic effects, the following text should be revised:

This drug has teratogenic effects; therefore, women of reproductive potential must be made aware of the following cautionary points before use.

1. This drug has been reported to cause teratogenicity.
2. Pregnancy tests must be conducted prior to initiating treatment with this drug and test results must be negative.
3. Contraception must be utilized before, during, and for 6 weeks after stopping treatment with this drug.
4. Patients should be periodically checked by consultations and repeated pregnancy tests, etc. to ensure that no pregnancy occurs during the administration of this drug. If pregnancy is suspected, the patient should immediately contact the doctor in charge.

In the Use in Pregnant, Parturient and Nursing Women section regarding pregnant women or women of reproductive potential, the following text should be revised:

This drug should not be administered to pregnant women or women suspected of being pregnant. [Teratogenicity including those of the ears (external auditory canal atresia, microtia, etc.), eyes (coloboma, microphthalmos, etc.), face (hypertelorism of the orbits, micrognathia, etc.), fingers (syndactyly, polydactyly, brachydactyly, etc.), heart (atrial and ventricular septal defect, etc.), esophagus (esophageal atresia, etc.), and nervous system (spina bifida, etc.) have been reported among patients taking this drug during pregnancy. Abortions have been reported in 45 to 49% of pregnant women exposed to this drug. Furthermore, in teratology studies, exencephaly, gastroschisis, etc. in rats (at 6 mg/kg/day), and patent ductus arteriosus, thoracoschisis, gastroschisis, etc. in rabbits (at 90 mg/kg/day) have been reported.]

In the Use in Pregnant, Parturient and Nursing Women section regarding pregnant women or women of reproductive potential, the following texts should be deleted:

As a general rule, this drug should not be administered to women of reproductive potential; however, if administration is absolutely necessary, the drug should only be administered if it is determined that treatment benefits outweigh the associated risks.

5. Closing comments

In administering mycophenolate mofetil to women of reproductive potential, please ensure that the safety measures described in this section are taken, and continue to comply with the proper use of mycophenolate mofetil. Please also refer to the materials for healthcare professionals and materials for patients on the proper use of mycophenolate mofetil that the MAH has prepared.

<Reference>
PMDA, Report on the Investigation Results. March 1, 2016.
http://www.pmda.go.jp/files/000211689.pdf

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Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated July 5, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Nintedanib Ethanesulfonate

Brand name (name of company)	Ofev Capsules 100 mg, 150 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Miscellaneous metabolism agents-Miscellaneous
Indications	Idiopathic pulmonary fibrosis

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Thrombocytopenia:** There have been reports of thrombocytopenia, including serious cases leading to bleeding. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 1 month (April 2013 to May 2016). Platelets (Plt) decreased-related cases: 3 cases (1 fatal case) The number of patients using the drug estimated by the MAH: Approximately 1 800 (August 2015 to April 2016) Launched in Japan: August 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Idiopathic pulmonary fibrosis (none)	300 mg for 35 days	**Thrombocytopenia, respiratory failure, pulmonary alveolar haemorrhage** Medical history: thalamus haemorrhage, interstitial lung disease 1 day before administration The patient was admitted to a hospital in order to start home oxygen therapy (HOT). Day 1 of administration Administration of this drug was started. Day 14 of administration Mild increases in hepatic function test levels (non-serious) occurred. A mild decrease in platelet count occurred. As symptoms stabilized, the patient was discharged. Day 35 of administration (day of discontinuation) Due to haemoptysis, the patient made an

				emergency outpatient visit. Due to respiratory distress and thrombocytopenia (Plt: 7000/μL) the subject was admitted. As pulmonary alveolar haemorrhage was also observed, steroid pulse therapy (methylprednisolone sodium succinate 1000 mg/day, Day 35 to Day 37 of administration) was performed. Infusion of Plt was started (10 units). Noninvasive positive-pressure ventilation (NPPV) was started. Administration of this drug was discontinued. 1 day after discontinuation Plt were transfused (10 units). 2 days after discontinuation Plt were transfused (10 units). 3 days after discontinuation The patient did not wish to be intubated for mechanical ventilation, and died of respiratory failure due to pulmonary alveolar haemorrhage.
	Concomitant medications: olmesartan medoxomil/azelnidipine			

Laboratory examination

	1 month before administration	1 day before administration	Day 7 of administration	Day 9 of administration	Day 13 of administration	Day 24 of administration	Day 35 of administration	1 day after discontinuation	2 days after discontinuation
T-bil (mg/dL)	0.48	0.51	0.46	0.56	0.55	0.33	0.85	–	1.10
AST (IU/L)	39	37	63	81	61	87	62	–	51
ALT (IU/L)	20	18	53	58	53	82	40	–	36
BUN (mg/dL)	14	11	12	–	11	14	12	–	25
Cre (mg/dL)	0.75	0.78	0.74	–	0.68	0.73	0.68	–	0.60
WBC (cells/μL)	8700	6900	6100	–	5700	6300	11300	12900	10900
Hb (g/dL)	14.9	15.1	14.5	–	13.9	14.7	12.6	11.0	10.0
Plt (x 10 000	16.4	17.0	11.7	–	11.0	9.6	0.7	0.3	0.3
Fibrin D dimer	–	–	–	–	–	–	2.18	–	1.88

2 Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir

Brand name (name of company)	Viekirax Combination Tablets (AbbVie GK)
Therapeutic category	Antivirals
Indications	Improvement of viremia in Serological Group 1 (Genotype 1) chronic hepatitis C or compensated cirrhosis C

PRECAUTIONS (underlined parts are revised)

Important precautions

Prior to the start of administration of this drug and periodically during treatment, renal function tests (serum creatinine, BUN, etc.) should be performed. Renal function may suddenly deteriorate in particular patients with decreased renal function and patients concomitantly administered calcium channel blockers. Therefore, these patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Adverse reactions (clinically significant adverse reactions)	**Acute renal failure**: Acute renal failure may occur. Patients should be carefully monitored through periodic renal function tests, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 1 month (April 2013 to May 2016). Acute renal failure-related cases: 9 cases (1 fatal case) The number of patients using the drug estimated by the MAH: Approximately 3000 (November 2015 to April 2016) Launched in Japan: November 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Hepatitis C (hypertension, diabetes mellitus, diabetic nephropathy, cryoglobulinaemia, nephrotic syndrome, glomerulonephritis membranoproliferative, hyperkalaemia)	2 tablets for 6 days	**Renal disorder, hypotension, multi-organ failure** 17 years before administration Treatment for hypertension and diabetes mellitus was started. The patient was found to be HCV positive. Liver supportive therapy was administered. 9 years before administration Right hemicolectomy was performed. Liver biopsy resulted in a pathological diagnosis of chronic hepatitis C, F2, A2. Treatment for hypertension, diabetes mellitus, and chronic hepatitis C was continued, and these conditions were under control. 4 months before administration Lower limb oedema occurred. From the findings urinary occult blood (-), urinary protein 4+, and albumin (Alb) 2.8, nephrotic syndrome was suspected. 2 months before administration The patient was admitted to the nephrology department. A kidney biopsy showed findings of glomerulonephritis membranoproliferative due to diabetic nephropathy and cryoglobulinaemia vasculitis, and nephrotic syndrome was diagnosed. Treatment with Predonine 30 mg was started, and as an improvement in complement levels and a decrease in urinary protein were observed, the dose of Predonine was reduced to 25 mg and the patient was discharged. Calcium channel blockers (CCBs), angiotension receptor blockers (ARBs), and alpha and beta blockers were required as therapy for hypertension, and hypertension was not under control. 14 days before administration The patient made an outpatient visit to the prescribing physician for treatment of HCV. Plt 143 000, prothrombin time (PT) 121.1%. From blood tests and clinical symptoms, the condition was judged to be F2 or F3.

				1 day before administration The patient was admitted to a hospital for liver biopsy (results have not been obtained). Blood pressure (BP) 136/77, lower limb oedema present. Abdominal ultrasound findings: Findings of strong fibrosis. Day 1 of administration Administration of this drug was started. Administration of concomitant medications including nifedipine was continued at the same doses. Calcium polystyrene sulfonate was added to the prescription. Day 2 of administration BP 94/48-107/59. Day 3 of administration No change in lower limb oedema. BP 93/52-108/53. Day 4 of administration BP 82/46-90/50. The patient experienced a fall on 2 occasions. A head computed tomography (CT) scan showed no abnormalities. Oral intake was poor. Day 5 of administration BP 82/51-94/55. Day 6 of administration (day of discontinuation) BP 66/32, total protein (TP) 4.3, Alb 2.2, aspartate aminotransferase (AST) 23, alanine aminotransferase (ALT) 43, total bilirubin (T-bil) 1.04, direct bilirubin (D-bil) 0.66, blood urea nitrogen (BUN) 108.8, creatinine (Cr) 5.01, estimated glomerular filtration rate (eGFR) 9.5, PT 114.9%. Acute renal failure occurred and the patient was transferred to another hospital for dialysis therapy. At the time of transfer, BP was less than 80, and therefore administration of dopamine hydrochloride was started, and BP increased to approximately 90. The findings TP 4.4, Alb 2.0, uric acid (UA) 9.0, and urinary protein/Cr ratio decreased to 0.5 (previously approximately 4.0) suggested a marked drop in renal blood flow. All oral medications including this drug were discontinued. Predonine 60 mg was administered, and fluid loading by transfusion was performed, but the patient's condition was close to anuria, with urine output of 280 mL. 1 day after discontinuation Continuous hemodiafiltration (CHDF) was started. 2 days after discontinuation CHDF was performed, but there was little response, and BP gradually decreased. In addition to dopamine hydrochloride, noradrenaline was administered, but it became impossible to maintain BP, and CHDF was discontinued. The patient's respiratory state aggravated, and endotracheal intubation and mechanical ventilation were performed. Pulse therapy with methylprednisolone 250 mg was also administered, but the patient's condition

				did not improve. 3 days after discontinuation At 21:43, the patient died of multi-organ failure due to drug-induced renal disorder associated with marked function kidney decreased and refractory hypotension likely to have been caused by a drug interaction between this drug and calcium antagonists. Autopsy was not performed. Pathological test were performed on the liver and kidneys (results not obtained).
Concomitant medications: nifedipine, azilsartan, carvedilol, ursodeoxycholic acid, monoammonium glycyrrhizinate/glycine/DL-methionine combination drug, calcium polystyrene sulfonate, febuxostat, prednisolone, famotidine, alogliptin benzoate, miglitol, repaglinide, insulin detemir (genetical recombination)				

Laboratory examination

	14 days before administration	Day 6 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation
White blood cell count	9200	7800	5380	5560	6550
Red blood cell count	357	318	343	340	295
Hemoglobin (g/dL)	11.6	10.4	11.2	11.0	9.6
Hematocrit (%)	32.6	29.0	33.1	32.1	28.1
Platelet count	14.3	16.9	19.0	16.1	14.5
Urea nitrogen (serum) (mg/dL)	36.5	108.8	119	96	55
Serum creatinine (mg/dL)	1.23	5.01	5.17	3.83	2.16
eGFR	44.1	9.5	9.18	12.74	23.84
Uric acid (serum) (mg/dL)	–	9.0	8.8	5.7	2.0
Sodium (mEq/L)	140	135	135	137	137
Chloride (mEq/L)	106	99	99	101	102
Potassium (mEq/L)	6.0	6.3	6.6	5.5	4.5
Total protein (serum) (g/dL)	5.0	4.3	4.4	4.6	4.4
Albumin (serum) (g/dL)	2.4	2.2	2.0	1.9	1.7
AST (U/L)	40	23	21	15	16
ALT (U/L)	63	43	46	38	29
Total bilirubin (mg/dL)	0.53	1.04	0.8	0.8	0.6
Direct bilirubin (mg/dL)	0.11	0.66	–	–	–
C-reactive protein (mg/dL)	–	0.07	1.40	5.00	3.23
Blood sugar (glucose) (mg/dL)	206	–	158	187	199
Hemoglobin A1c (HbA1c) (%)	6.7	–	–	–	–
Prothrombin time (%)	121.1	114.9	–	–	–
Urine specific gravity	–	1.017	1.013	1.017	1.021
pH	–	5.0	5.0	5.0	5.0
Urinary protein		(2+)	(1+)	(1+)	(2+)
Urinary occult blood (hemoglobin)		(-)			
Urinary occult blood (red blood cells)		(-)			

3 (1) Sofosbuvir
(2) Ribavirin

Brand name (name of company)	(1) Sovaldi Tablets 400 mg (Gilead Sciences K.K.) (2)Rebetol Capsules 200 mg (MSD K.K.), Copegus 200 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic category	Antivirals
Indications	1. Improvement of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C virus (HCV) infection or compensated cirrhosis C 2. Rebetol Capsules 200 mg 1. Improvement of viremia when used concomitantly with interferon alfa-2b (genetical recombination), peginterferon alfa-2b (genetical recombination), or interferon beta in any of the following patients with chronic HCV infection: (1) Patients with high blood HCV RNA load (2) Patients who have failed to respond to, or have relapsed after, interferon monotherapy 2. Improvement of viremia when used concomitantly with peginterferon alfa-2b (genetical recombination) in patients with compensated cirrhosis C 3. Improvement of viremia when used concomitantly with sofosbuvir in patients with serogroup 2 (genotype 2) chronic HCV infection or compensated cirrhosis C Copegus 200 mg 1. Improvement of viremia when used concomitantly with interferon alfa-2a (genetical recombination) in any of the following patients with chronic HCV infection: (1) Serogroup 1 (genotype I [1a] or II [1b]) patients with high HCV RNA loads (2) Patients who have failed to respond to, or have relapsed after, interferon monotherapy 2. Improvement of viremia when used concomitantly with peginterferon alfa-2a (genetical recombination) in patients with compensated cirrhosis C 3. Improvement of viremia when used concomitantly with sofosbuvir in patients with serogroup 2 (genotype 2) chronic HCV infection or compensated cirrhosis C

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Hypertension: Hypertension may occur. Cases of systolic blood pressure greater than or equal to 180 mmHg or diastolic blood pressure greater than or equal to 110 mmHg have been reported with this drug. Patients should be carefully monitored through changes in blood pressure, etc., during administration of this drug. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Cerebrovascular disorder: Cerebrovascular disorders, such as cerebral infarction and cerebral hemorrhage, may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 1 month (April 2013 to May 2016).
Hypertension-related cases: 1 case (0 fatal cases), cerebrovascular disorder-related cases: 8 cases (0 fatal cases)
The number of patients using the drug estimated by the MAH:
(1)Approximately 36 000 (May 2015 to April 2016)
(2)Approximately 37 000 (July 2015 to April 2016)
Launched in Japan:
(1) Rebetol Capsules 200 mg: May 2015
(2) Copegus 200 mg: December 2001

Case summary: Sofosbuvir and Ribavirin

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Hepatitis C (none)	400 mg for 8 days	**Adverse reactions: hypertension, hypokalaemia, tachycardia** History of hypertension: none Alcohol intake: social drinker, smoker Unknown date Heart rate 60/min Day 1 of administration Administration of sofosbuvir and ribavirin was started. Potassium (K) 3.8 mEq/L, BP 150 mmHg Day 8 of administration (day of discontinuation) Hypertension, hypokalaemia, and tachycardia occurred, and therefore the patient was admitted to a hospital. Administration of sofosbuvir and ribavirin was discontinued. BP 211/115 mmHg, heart rate 132/min, K 3.0 mEq/L Spironolactone and nifedipine were administered for hypertension, hypokalaemia, and tachycardia. 1 day after discontinuation BP 124/62 mmHg, heart rate 60/min, K 3.9 mEq/L. The outcome of hypertension, hypokalaemia, and tachycardia recovered. 4 days after discontinuation The patient was discharged. Sofosbuvir was not readministered.
	Concomitant medications: ribavirin, loxoprofen sodium hydrate, fursultiamine hydrochloride, rebamipide, famotidine, isoleucine/leucine/valine, brotizolam			

Laboratory examination

	Before administration (date unknown)	After administration	Day 8 of administration (day of discontinuation)	1 day after discontinuation
Heart rate (/min)	60	—	132	60
Blood pressure (mmHg)	—	150	211/115	124/62
Potassium (mEq/L)	—	3.8	3.0	3.9

4 Ledipasvir Acetonate/Sofosbuvir

Brand name (name of company)	Harvoni Combination Tablets (Gilead Sciences K.K.)
Therapeutic category	Antivirals
Indications	Improvement of viremia in patients with serogroup 1 (genotype 1) chronic HCV infection or compensated cirrhosis C

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Hypertension: Hypertension may occur. Cases of systolic blood pressure greater than or equal to 180 mmHg or diastolic blood pressure greater than or equal to 110 mmHg have been reported with this drug. Patients should be carefully monitored through changes in blood pressure, etc., during administration of this drug. If any abnormalities are observed, appropriate measures such as discontinuation of administration drug should be adopted.

Cerebrovascular disorder: Cerebrovascular disorders, such as cerebral infarction and cerebral hemorrhage, may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 1 month (April 2013 to May 2016).
Hypertension-related cases: 5 cases (0 fatal cases), cerebrovascular disorder-related cases: 11 cases (0 fatal cases)
The number of patients using the drug estimated by the MAH:
Approximately 77 000 (September 2015 to May 2016)
Launched in Japan:
September 2015

Case summary: Harvoni Combination Tablets

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
	Female 60s	Chronic hepatitis C (quadriparesis, sensory disturbance, hemianopia)	1 tablet 84 days	**Adverse reactions: cerebral haemorrhage, hypertension** Medical history: gastrointestinal submucosal tumor, alcohol consumption: yes, non-smoker Approximately 35 years to 25 years before administration The patient contracted hepatitis C from blood transfusion. Approximately 18 months to 15 days before administration Peg-interferon alfa-2a was administered twice per month. Examination before administration BP 140 mmHg Day 1 of administration Administration of this drug was started. Day 14 of administration From the evening, a sensation of heaviness of head appeared, and the patient also experienced feels poorly, swaying, and disorganized thinking. BP 200 mmHg (measured at home) The patient took amlodipine besilate, prescribed for a family member, and her BP decreased to 180 mmHg. Day 15 of administration Consciousness disturbed was present.

				Day 16 of administration As swaying when walking continued until morning, the patient was transported to the hospital as an emergency case. A head CT scan performed at the hospital found a subcortical haemorrhage in the left parietal lobe. Head CT and magnetic resonance imaging (MRI) scans found no obvious source of bleeding such as haemanginoma or artery malformation. As BP was high, 150 mmHg to 170 mmHg, cerebral haemorrhage due to hypertension was diagnosed, and the patient was admitted. Unknown date This drug was suspended for 2 days (reason unknown). Unknown date After admission, tranexamic acid, carbazochrome, and nicardipine hydrochloride were administered continuously for 2 days. After administration of nicardipine hydrochloride ended, BP remained high. Rehabilitation was performed, while administration of this drug was continued. Day 25 of administration No problems occurred during an experimental overnight stay at home, and therefore, instead of returning to the hospital, the patient was discharged. Day 52 of administration Administration of amlodipine besilate (1 tablet) was started for hypertension. Unknown date BP was approximately 150 mmHg. The dose of amlodipine besilate was increased to 2 tablets twice per day. Day 86 of administration Treatment with this drug was complete (suspended for 2 days). Outcome: Cerebral haemorrhage resolved with sequelae. Hypertension was resolving.
	Concomitant medications: sennoside			

Laboratory examination

	Examination before administration	Day 14 of administration	Day 16 of administration	Unknown date
Blood pressure (mmHg)	140	200* 180**	150 to 170	Approximately 150

*: Measured at home
**: After taking amlodipine besilate

3

Revision of Precautions (No. 276)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated July 5, 2016.

1

Anti-inflammatory agents

Diclofenac sodium (oral, suppository, enema ointment)

Brand name	(1) Voltaren Tablets 25 mg (Novartis Pharma K.K.), and others (2) Voltaren SUPPO 12.5 mg, 25 mg, 50 mg (Novartis Pharma K.K.), Rectos enema ointment 25 mg, 50 mg (Nichi-Iko Pharmaceutical Co., Ltd.), and others (3) Voltaren SR Capsules 37.5 mg (Dojin Iyaku-Kako Co., Ltd.), and others
Adverse Reactions (clinically significant adverse reactions)	**Gastrointestinal stenosis / obstruction:** Stenosis or obstruction may occur in association with gastrointestinal ulcer.

2

Pituitary hormone preparations

Oxytocin

Brand name	Atonin-O Injection 1 unit, 5 units (ASKA Pharmaceutical Co., Ltd.), and others
Adverse Reactions (clinically significant adverse reactions)	**Shock and anaphylaxis:** Shock and anaphylaxis may occur. Patients should be carefully monitored. If abnormalities such as decreased blood pressure, rash, redness, itching, angioedema, dyspnea, and cyanosis are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

3

Epidermides-Miscellaneous

Benzoyl peroxide

Brand name	Bepio Gel 2.5% (Maruho Co., Ltd.)
Important Precautions	Skin exfoliation (scales, desquamation), erythema, irritation, and swelling, etc., may occur during administration of this drug. There have been reports of erythema and swelling spreading to the entire face and neck. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

4

Epidermides-Miscellaneous

Clindamycin phosphate hydrate / benzoyl peroxide

Brand name	Duac Combination Gel (Pola Pharma Inc.)
Important Precautions	Skin exfoliation, erythema, irritation, and swelling, etc., may occur during administration of this drug. There have been reports of erythema and swelling spreading to the entire face and neck as well as serious blister and erosion. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

5

Anticoagulants

Apixaban

Brand name	Eliquis Tablets 2.5 mg, 5 mg (Bristol-Myers Squibb K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic function disorder:** Hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

6

Miscellaneous metabolism agents-Miscellaneous

Fingolimod hydrochloride

Brand name	(1) Imusera Capsules 0.5 mg (Mitsubishi Tanabe Pharma Corporation) (2) Gilenya Capsules 0.5 mg (Novartis Pharma K.K.)
Precautions for Indications	The efficacy and safety of this drug for progressive multiple sclerosis have not yet been established. Fingolimod did not slow progression of physical disability in an overseas placebo-controlled study in patients with primary progressive multiple sclerosis.
Other Precautions	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 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). <Reference> Lublin, F., et al.: Lancet 2016;387:1075-1084

7

Alkylating agents

Carmustine

Brand name	Gliadel for Intracerebral Implant 7.7 mg (Eisai Co., Ltd.)
Important Precautions	Air accumulation may occur at the implant site, and there have been reports of neurological symptoms. After the implantation of the drug, neurological symptoms, such as hemiplegia, aphasia, and disturbed consciousness, should be carefully monitored. If any abnormalities are observed, appropriate measures should be adopted.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the adverse drug reaction (ADR) from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of June 30, 2016)

◎: Products for which EPPV was initiated after June 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Octocog Beta (Genetical Recombination) Kovaltry for iv injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin, Ltd.	June 29, 2016
◎	Bexarotene Targretin Capsules 75 mg	Minophagen Pharmaceutical Co., Ltd.	June 23, 2016
◎	Maxacalcitol/betamethasone butyrate propionate Marduox Ointment	Chugai Pharmaceutical Co., Ltd.	June 21, 2016
◎	Primaquine Phosphate Primaquine Tablets 15 mg	Sanofi K.K.	June 17, 2016
◎	Dutasteride (1) Zagallo Capsules 0.1 mg (2) Zagallo Capsules 0.5 mg	GlaxoSmithKline K.K.	June 13, 2016
◎	Mepolizumab (Genetical Recombination) Nucala for Subcutaneous Injection 100 mg	GlaxoSmithKline K.K.	June 7, 2016
◎	Radium (^{223}Ra) Chloride Xofigo Injection	Bayer Yakuhin, Ltd.	June 1, 2016
◎	Rurioctocog Alfa Pegol (Genetical Recombination) Adynovate Intravenous 250, 500, 1000, 2000	Baxalta Japan Ltd.	June 1, 2016
◎	Trametinib Dimethyl Sulfoxide Mekinist Tablets 0.5mg, 2mg	Novartis Pharma K.K.	June 1, 2016
◎	Dabrafenib Mesilate Tafinlar Capsules 50mg, 75mg	Novartis Pharma K.K.	June 1, 2016
	Perampanel Hydrate Fycompa Tablets 2 mg, 4 mg	Eisai Co., Ltd.	May 26, 2016
	Asenapine Maleate Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.	May 26, 2016
	Sebelipase Alfa (Genetical Recombination) Kanuma Injection for Intravenous 20 mg	Alexion Pharma G.K.	May 25, 2016
	Osimertinib Mesilate Tagrisso Tablets 40 mg, 80 mg	AstraZeneca K.K.	May 25, 2016

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Ceritinib Zykadia Capsules 150 mg	Novartis Pharma K.K.	May 25, 2016
Ibrutinib Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	May 25, 2016
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg*1	Teijin Pharma Limited	May 23, 2016
Botulinum Toxin Type A Botox Vista Injection 50 Units*2	Allergan Japan K.K.	May 23, 2016
Iloprost Ventavis Inhalation Solution 10 μg	Bayer Yakuhin, Ltd.	May 16, 2016
Methacholine Chloride (1) Provocholine Powder for Inhalation Solution 100 mg (2) Kenbran Powder for Inhalation Solution 100 mg	(1) Sanwa Kagaku Kenkyusho Co., Ltd. (2) Santen Pharmaceutical Co., Ltd.	May 10, 2016
Nonacog Gamma (Genetical Recombination) Rixubis Intravenous 250, 500, 1000, 2000, 3000	Baxter Limited	May 9, 2016
Luliconazole Luconac Solution 5% *3	Sato Pharmaceutical Co., Ltd.	April 25, 2016
Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016
Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016
Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg *4	Shionogi & Co., Ltd.	March 18, 2016
Eribulin Mesilate Halaven Intravenous Injection 1 mg*5	Eisai Co., Ltd.	February 29, 2016
Risperidone Risperdal Tablets 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL *6	Janssen Pharmaceutical K.K.	February 29, 2016
Rituximab (Genetical Recombination) Rituxan Injection 10 mg/mL*7	Zenyaku Kogyo Co., Ltd.	February 29, 2016
Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016
Indium pentetreotide (111In) OctreoScan Kit for Intravenous Use	FUJIFILM RI Pharma Co., Ltd.	January 27, 2016
Esflurbiprofen/Mentha oil Loqoa Tape	Taisho Pharmaceuticals Co., Ltd.	January 21, 2016
Bosentan hydrate Tracleer 32 mg dispersible tablets for pediatrics	Actelion Pharmaceuticals Japan Ltd.	January 12, 2016
Ozenoxacin Zebiax Lotion 2%	Maruho Co., Ltd.	January 7, 2016

*1 Hyperuricemia associated with cancer chemotherapy

*2 Lateral canthal lines in adult patients under the age of 65

*3 Nail tinea

*4 Pain associated with chronic lumbago

*5 Malignant soft tissue sarcoma

*6 Irritability associated with autism spectrum disorder in childhood

*7 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants