

Report on the Investigation Results

March 1, 2016

Pharmaceuticals and Medical Devices Agency

I. Overview of Product

[Non-proprietary name]	Mycophenolate Mofetil
[Brand name]	(a) CellCept Capsules 250, and CellCept Powder for Suspension 31.8% (b) Mycophenolate Mofetil Capsules 250 mg Teva (c) Mycophenolate Mofetil Capsules 250 mg Pfizer
[Approval holder]	(a) Chugai Pharmaceutical Co., Ltd. (b) Teva Pharma Japan Inc. (c) Mylan N.V.
[Indications]	○ Treatment of refractory organ rejection 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 rejection of renal transplants, cardiac transplants, hepatic transplants, lung transplants, or pancreas transplants
[Dosage and administration]	1. Renal transplants ○ Treatment of refractory organ rejection in patients who received renal transplants The usual adult dosage is 1500 mg of mycophenolate mofetil orally administered twice daily, every 12 hours after meals. The dose may be adjusted according to the patient's age and condition. ○ Prophylaxis against rejection in renal transplantation Adults: The usual dosage is 1000 mg of mycophenolate mofetil orally administered twice daily, every 12 hours after meals. The dose may be adjusted according to the patient's age and condition; however, the total daily dose should not exceed 3000 mg.

Pediatrics: The usual dosage is 300 to 600 mg/m² of mycophenolate mofetil orally administered twice daily, every 12 hours after meals. The dose may be adjusted according to the patient's age and condition; however, the total daily dose should not exceed 2000 mg.

2. Prophylaxis against rejection of cardiac, hepatic, lung, or pancreas transplants

The usual adult dosage is 500 to 1500 mg of mycophenolate mofetil orally administered twice daily, every 12 hours after meals.

However, the tolerance dose or effective dose of the drug differs from one patient to another; therefore, the dose needs to be carefully adjusted to achieve an optimum therapeutic effect.

[Items warranting special mention] None

[Investigating office] Office of Safety II

II. Background of the investigation

1. Status in Japan

Mycophenolate mofetil, a pro-drug of mycophenolic acid, the active moiety, is an immunosuppressive agent that suppresses lymphocyte proliferation through the inhibitory action of mycophenolic acid on nucleic acid synthesis. In Japan, CellCept Capsules 250 was approved in September 1999 with indications for treatment of refractory organ rejection in patients who received renal transplants (for patients diagnosed with refractory organ rejection for whom conventional therapy is ineffective or inappropriate due to adverse reactions). Subsequently, indications for prophylaxis against rejection of renal, cardiac, hepatic, lung, and pancreas transplants were added, and mycophenolate mofetil has been widely used in the field of transplantation. In August 2015, an additional dosage form, CellCept Powder for Suspension 31.8%, was approved.

The public knowledge-based application for mycophenolate mofetil was subjected to preliminary evaluation at the meeting of First Committee on Drugs, Pharmaceutical Affairs and Food Sanitation Council, held on July 31, 2015, and the use of the drug for the treatment of lupus nephritis was to be covered by health insurance from that date. Also, "Points to be Considered When Using Mycophenolate Mofetil" (PFSB/ELD Notification No. 0731-7, and

PFSB/Safety Division Notification No. 0731-4, dated July 31, 2015) was issued to provide caution on teratogenicity of the drug.

Since the time of approval, 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 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.

In view of the situation, on February 26, 2016, the Safety Division, Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare requested PMDA to conduct investigation regarding pregnancy and contraception relating to administration of mycophenolate mofetil. In this investigation, PMDA studied the validity of current safety measures and necessity for implementing further safety measures based on concerns over issues of pregnancy and contraception in women exposed to mycophenolate mofetil.

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

2. Status in other countries

CellCept Capsules 250 has been approved and marketed in 125 or more countries including the US and Europe. In European countries and the US, mycophenolate mofetil is indicated only for transplant-related conditions, and indications for lupus nephritis have not yet been approved.

In the package insert of CellCept marketed in the US, pregnant women and women of

reproductive potential are not listed in the "CONTRAINDICATIONS" section, and cautionary statements on contraception and pregnancy testing are provided in the "PRECAUTIONS" section. The prescribing information was revised in July 2015 to include nervous system malformations in the "WARNING" and "Pregnancy" sections, and reported congenital malformations, including ear, facial, cardiac and nerve system malformations, in the children of patients who received the drug during pregnancy in the "Postmarketing Experience" section.

In Europe, the package insert was revised in January 2016 to include new contraindications: women of childbearing potential who are not using highly effective contraception, women of childbearing potential without provision of a negative pregnancy test result, and pregnant women unless there is no suitable alternative treatment. New statements were also added in the "Special warnings and precautions for use" section, including that female and male patients of reproductive potential should be made aware of the risks and follow the recommendations on contraceptive methods and pregnancy planning, and female patients of reproductive potential should use 2 contraceptive methods during treatment and for 6 weeks after stopping treatment. Further, in the "Pregnancy and lactation" section, the following information was included: a pregnancy test should be performed; congenital malformations (ear, congenital heart diseases, facial, eye, fingers, tracheo-oesophageal, nervous system, renal, microphthalmia, congenital choroid plexus cyst, septum pellucidum agenesis, olfactory nerve agenesis) including multiple malformations have been reported in post-marketing surveillance in children of patients who were exposed to CellCept in combination with other immunosuppressants.

III. Summary of data submitted by the marketing authorization holder of the product

The marketing authorization holder (Chugai Pharmaceutical Co., Ltd.) revised the Company Core Data Sheet (CCDS) in October 2015, and a Drug Safety Report concerning exposure to CellCept during pregnancy was submitted. The following paragraphs describe the outline of the report.

A review of congenital abnormalities reported in and outside Japan 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.), oesophageal malformations (oesophageal 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, treatment had been discontinued within 8 weeks of the last menstrual period before pregnancy in approximately 75% of these patients. 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. Eight malformations were observed (including 2 selective terminations). It was estimated that the incidence of malformations is 26%, and the probability of spontaneous abortion is 45% (*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 11 malformations (23%) were observed (*Clin Transpl.* 2009;103-122).

IV. Summary of investigation by PMDA

1. Administration of mycophenolate mofetil to women of reproductive potential

Based on the reports on teratogenic effects of mycophenolate mofetil in humans and revisions of package inserts in other countries, PMDA's considerations are as follows:

To avoid pregnancy while on mycophenolate mofetil, it is necessary to ensure that patients utilize reliable contraception methods prior to initiation through to 6 weeks after stopping treatment with this drug, and caution should be advised with a greater emphasis on conducting pregnancy tests on a regular basis. On the other hand, the use of mycophenolate mofetil for the treatment of lupus nephritis is covered by health insurance, and given that women aged between their 20s and 40s are affected more frequently than other groups by lupus nephritis, mycophenolate mofetil can be offered as a treatment option for women of reproductive potential by ensuring that contraception is used and conducting pregnancy tests in a strict manner to prevent drug intake in pregnant women.

Based on the above points, PMDA concluded that "Women of reproductive potential" should be deleted from the "RELATIVE CONTRAINDICATIONS" section in the package insert, and cautionary statements on contraception and pregnancy testing currently included in the "Important Precautions" section should be added to the "WARNING" section. At the same time, it is appropriate to add a new cautionary statement to the effect that pregnancy tests should be

performed to confirm that the patients are not pregnant on a regular basis to ensure that exposure of pregnant women to mycophenolate mofetil is prevented.

As in the current package insert, the mention of pregnant women or women suspected of being pregnant should be in the "CONTRAINDICATIONS" section, and caution should be continuously advised.

2. Implementation of pregnancy tests on a regular basis during treatment

In the current package insert, it is stated in the "Important Precautions" section that a negative pregnancy test result should be obtained before starting treatment with mycophenolate mofetil.

To avoid exposure of pregnant women to mycophenolate mofetil, PMDA considers appropriate to clearly state in the "Important Precautions" section that it is desirable for patients to have regular pregnancy tests during the administration of this drug, and if pregnancy is suspected, the patient should immediately contact the doctor in charge.

3. Teratogenic effects

In the current package insert, the "Use in pregnant, parturient and nursing women" section has the description "congenital malformations including ear malformations have been reported in children of patients who took mycophenolate mofetil during pregnancy in combination with other immunosuppressants."

Given that the data submitted by the marketing authorization holder showed that in addition to ear malformations, eye, facial, finger, cardiac, oesophageal, nervous system, and other malformations have also been reported, PMDA considers that it is appropriate to add a statement to the effect that "teratogenicity 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." PMDA also considers that the phrase "in combination with other immunosuppressants" should be deleted from the current description, because reported cases of malformations included cases in which no other immunosuppressants were administered in combination.

4. Abortions

Currently, no caution has been advised with regard to abortion in the package insert.

However, 1 case each of spontaneous abortion and fetal death have been reported in Japan. Further, the incidence of abortion (45% to 49%) reported in the literature included in the data submitted by the marketing authorization holder (*Am J Med Genet A.* 2012;158A: 588-596; and *Clin Transpl.* 2009;103-122) is significantly higher compared with the generally reported incidence of spontaneous abortion (8% to 15%, Igaku-shoin's Medical Dictionary, second edition, 2009).

Based on the incidence and information in the package inserts of other countries, PMDA concluded that it is appropriate to include a statement to the effect that "Abortions have been reported in 45% to 49% of pregnant women exposed to this drug among patients taking this drug during pregnancy" in the "Use in pregnant, parturient and nursing women" section

The conclusion of PMDA described above was supported by the expert advisors at the Expert Discussion, including that "Women of reproductive potential" should be deleted from the "RELATIVE CONTRAINDICATIONS" section in the package insert, and a new cautionary statement to the effect that pregnancy tests should be performed to confirm that the patients are not pregnant on a regular basis during treatment should be added to the "WARNING" section in addition to cautionary statements on contraception and pregnancy testing prior to initiating treatment currently included in the section.

Further, the following issues were commented by expert advisors: while it is necessary to check that the patient is not pregnant at the start of treatment and on a regular basis during treatment, it is questionable why only pregnancy testing is emphasized as the method of confirmation. Performing pregnancy tests means that reliable contraception methods have not been implemented.

In view of the comments of the expert advisors, PMDA's considerations are as follows:

To avoid exposure of pregnant women to mycophenolate mofetil, it is essential to make sure that contraception is utilized. In addition, it is also necessary to confirm that the patient is not pregnant during treatment. Pregnancy testing is one of the useful methods to confirm this, however, methods of confirmation are not necessarily limited to pregnancy testing.

In the current package insert, caution on contraception and pregnancy tests is included in the "Important Precautions" section with other caution on adverse reactions such as symptoms of

infection, and bone marrow suppression, and on skin cancer, as part of information to be provided to "patients or other appropriate persons representing patients." However, in order to prevent exposure of pregnant women to mycophenolate mofetil, caution on pregnancy testing and contraception should be stated separately in the "Important Precautions" section, and it is appropriate to state clearly the information on the use of mycophenolate mofetil to women of reproductive potential as issues to be explained to, and understood by patients themselves.

Based on the above, in addition to "reported to cause teratogenicity," "confirmation of negative pregnancy results before starting treatment," and "use of contraception before and during treatment, and for 6 weeks after stopping treatment" currently included in the "Important Precautions" section, it is appropriate to add a statement to the effect that "Patients should be periodically checked and monitored to ensure that no pregnancy occurs during the administration of this drug by consultations and repeated pregnancy tests, etc. If pregnancy is suspected, the patient should immediately contact the doctor in charge" as an issue to be explained to, and understood by patients when administering mycophenolate mofetil to women of reproductive potential.

V. Overall evaluation

PMDA concludes that that revision of the package insert was necessary with regard to descriptions on pregnancy and contraception related to mycophenolate mofetil.