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Report on Investigation Results

June 15, 2018
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Ciclosporin
[Branded name]	Sandimmum for I.V. Infusion 250 mg and the others (See Appendix)
[Approval holder]	Novartis Pharma K. K. and the others (See Appendix)
[Indications]	See Appendix
[Dosage and administration]	See Appendix
[Remarks]	Nothing noteworthy
[Investigating office]	Office of Safety II

II. Investigation background

Dystocia and perinatal death were observed as a result of animal reproductive toxicity studies of rats administered ciclosporin conducted at the time of the initial application for marketing authorization for this drug. Teratogenicity was also demonstrated in additional subsequent animal reproductive toxicity studies. Administration to “pregnant women or women who may be pregnant" is contraindicated according to the current package insert for the oral and injectable dosage forms of ciclosporin.

In May 2018, the Information Provision Working Group Committee at the Japan Drug Information Institute in Pregnancy (the Working Group), which was established as a project by the Ministry of Health, Labour and Welfare (MHLW) for the purpose of reflecting the latest knowledge with respect to pregnancy and other related issues in pharmaceutical product package inserts, concluded that administration to “pregnant women or women who may be pregnant” should be removed from the Contraindications section of the package insert of preparations containing ciclosporin and should be replaced with a precaution stating that such women “should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” as an appropriate revision of the package insert.

In response to a report prepared by the Working Group, on May 29, 2018, the Pharmaceutical Safety Division of the Pharmaceutical Safety and Environmental Health Bureau at MHLW requested an investigation of the revision of precautions regarding preparations containing ciclosporin proposed by the Working Group based on its report, to be conducted by the Pharmaceuticals and Medical Devices Agency (PMDA). PMDA accordingly evaluated the proposed revision of the relevant ciclosporin package insert.

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

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III. PMDA Investigation

The Working Group, taking into account the latest knowledge and the current medical environment, concluded in its report that revision of the package insert is appropriate for preparations containing ciclosporin, as follows:

1. Contraindication of the administration to “pregnant women or women who may be pregnant” in the current package insert of the oral and injectable dosage forms

For the oral and injectable dosage forms, a precaution stating that such women “should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” should be included in the 6. Use during Pregnancy, Delivery, or Breast-feeding section and language of "pregnant women or women who may be pregnant” should be removed from the Contraindications section.

2. Addition of risk information related to pregnancy

For the oral and injectable dosage forms, the current version states, in the 6. Use during Pregnancy, Delivery, or Breastfeeding section, that “teratogenic effects as well as dystocia and perinatal death have been reported in animal studies using rats.” In consideration of the clinical reports evaluated by the Working Group as well as statements contained in overseas package inserts, additionally including language concerning the reports on transfer across the placenta in humans as well as cases of premature birth or low birth weight baby, and cases involving delivery of neonates exhibiting congenital anomalies by women following organ transplantation was determined to be appropriate.

While the package insert of the ophthalmic solution of ciclosporin already includes a statement that “Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks”, the characteristic transfer of ciclosporin across the placenta in humans should be added together with the results of relevant animal studies.

PMDA concluded, based on the report of the Working Group and its own investigation, the proposed revision as the result of discussion in the Group may be properly adopted with some modifications of language.

In consideration of the precautionary language, “Women should be instructed to refrain from breastfeeding while receiving this drug” already included in 6. Use during Pregnancy, Delivery, or Breastfeeding section, PMDA decided that it should be appropriate to remove “breast-feeding women” from the Contraindications section of the package insert in order to maintain consistency with respect to administration of the oral and injectable forms of ciclosporin to breast-feeding women.

The above conclusion reached by PMDA was supported by its expert advisors.

IV. Overall evaluation

PMDA concluded that precautions in the package insert should be appropriately revised as follows:

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[Proposed revision] Ciclosporin (oral and injectable dosage forms)

Revised language is underlined

Current version	Proposed revision
[Contraindications (This drug should not be administered to the following patients)] 1. (snip) 2. Pregnant women, women who may be pregnant, or breast-feeding women (Refer to the Use during Pregnancy, Delivery, or Breastfeeding section.) 3., 4 (snip)	[Contraindications (This drug should not be administered to the following patients)] 1. (snip) (deleted) 2., 3 (snip)
[Precautions] 6. Use during Pregnancy, Delivery, or Breastfeeding (1) This drug should not be administered to pregnant women or women who may be pregnant. (Teratogenic effects, dystocia, and perinatal death have been reported in animal studies using rats.) (2) Women should be instructed to refrain from breastfeeding while receiving this drug. (Excretion into breast milk has been reported.)	[Precautions] 6. Use during Pregnancy, Delivery, or Breastfeeding (1) Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks [Teratogenic effects, dystocia, and perinatal death have been reported in animal studies using rats. Placental transfer in humans has been reported[3)-6)]. Premature birth cases and influence on the infants (low birth weight, congenital anomalies) have been reported in women who received this drug during pregnancy[7)].] (2) Women should be instructed to refrain from breastfeeding while receiving this drug. (Excretion into breast milk has been reported.)

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[References] 1)–2) (snip) (newly added) 3)–16) (snip)	[References] 1)–2) (snip) 3) Baxi LV et al. : Am J Obstet Gynecol. 169(1), 33,1993 4) Burrows DA et al. : Obstet Gynecol. 72(3), 459, 1988 5) Lowenstein BR et al. :Am J Obstet Gynecol. 158(3), 589, 1988 6) Flechner SM et al. : Am J Kidney Dis. 5(1), 60, 1985 7) Coscia LA et al. : Best Pract Res Clin Obstet Gynaecol 28(8), 1174, 2014 8)–21) (snip)

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[Proposed revision] Ciclosporin (ophthalmic solution)

Revised language is underlined

Current version	Proposed revision
[Precautions] 4. Use during Pregnancy, Delivery, or Breastfeeding 1) Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. (Safety in pregnant women has not been established) Animal studies (rats: Oral) have reported teratogenic effects, dystocia, and perinatal death) 2）(snip)	[Precautions] 4. Use during Pregnancy, Delivery, or Breastfeeding 1) Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. [Animal studies [rats: oral] have reported teratogenic effects, dystocia, and perinatal death. Placental transfer in humans (orally administered) has been reported[1)-4)].] 2）(snip)
(References) (newly added) 1)–6) (snip)	(References) 1) Baxi LV et a. l: Am J Obstet Gynecol. 169, 33 (1993) 2) Burrows DA et al. : Obstet Gynecol. 72, 459, (1988) 3) Lowenstein BR et al. : Am J Obstet Gynecol. 158, 589, (1988) 4) Flechner SM et al. : Am J Kidney Dis. 5, 60, (1985) 5)–10) (snip)

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Appendix

List of drugs investigated

As of June 2018

Branded name	Marketing authorization holder	Indications	Dosage and administration
Sandimmum for I.V. Infusion 250 mg	Novartis Pharma K. K.	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, pancreas, and small intestine transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation	This drug is diluted 1:100 with JP normal saline or JP glucose injection and administered as an intravenous infusion. 1. Kidney, bone marrow, heart, lung, and pancreas transplantation The usual daily dose is 3-5 mg/kg of ciclosporin from the day before transplantation. Patients should be switched to oral administration as soon as possible. 2. Liver, and small intestine transplantation The usual daily dose is 4-6 mg/kg of ciclosporin from the day before transplantation. Patients should be switched to oral administration as soon as possible.
Sandimmum Oral Solution 10%	Novartis Pharma K. K.	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, and pancreas transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation 3. Behcet's disease (involving ocular complications) 4. Vulgar psoriasis (refractory or affecting more than 30% of the skin surface),	1. Kidney transplantation The usual daily dose is 9-12 mg/kg of ciclosporin administered in one or two divided doses orally from the day before transplantation, then decreased by 2 mg/kg per day after that. The usual maintenance dose is 4-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 2. Liver transplantation The usual daily dose is 14-16 mg/kg of ciclosporin

Branded name	Marketing authorization holder	Indications	Dosage and administration
		pustular psoriasis, erythrodermic psoriasis, arthropathic psoriasis 5. Aplastic anaemia (severe), pure red cell aplasia 6. Nephrotic syndrome (frequently relapsing or steroid-resistant)	administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 5-10 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 3. Heart, lung, and pancreas transplantation The usual daily dose is 10-15 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 2-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 4. Bone marrow transplantation The usual daily dose is 6-12 mg/kg of ciclosporin administered in one or two divided doses orally from the day before transplantation. The dose should be maintained for 3-6 months before it is gradually decreased and discontinued. 5. Behcet's disease The usual daily dose starts at 5 mg/kg of ciclosporin administered in one or two divided doses orally, then is decreased or increased by 1-2 mg/kg/day monthly after that. The usual maintenance dose is 3-5 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients.

Branded name	Marketing authorization holder	Indications	Dosage and administration
			6. Psoriasis The usual daily dose is 5 mg/kg administered in two divided doses orally. If improvement is observed, the dose is decreased by 1 mg/kg/day monthly after that. The usual maintenance dose is 3 mg/kg daily. The dose may be adjusted depending on the symptoms of the patients. 7. Aplastic anaemia The usual daily dose is 6 mg/kg of ciclosporin administered in two divided doses orally. The dose may be adjusted depending on the symptoms of the patients. The treatment effects observed may be larger in patients with shorter duration of illness. It is preferable for this drug to be administered to patients with the duration of illness less than 6 months as a rule. 8. Nephrotic syndrome The usual daily dose of ciclosporin administered in two divided doses orally is as mentioned below. The dose may be adjusted depending on the symptoms of the patients. (1) Frequently relapsing cases For adult dose, 1.5 mg/kg is administered daily. For child dose, 2.5 mg/kg is administered daily.

Branded name	Marketing authorization holder	Indications	Dosage and administration
			(2) Steroid-resistant cases For adult dose, 3 mg/kg is administered daily. For child dose, 5 mg/kg is administered daily.
Sandimmum Capsules 25 mg, 50 mg	Novartis Pharma K. K.	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, and pancreas transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation 3. Behcet's disease (involving ocular complications) 4. Vulgar psoriasis (refractory or affecting more than 30% of the skin surface), pustular psoriasis, erythrodermic psoriasis, arthropathic psoriasis 5. Aplastic anaemia (severe), pure red cell aplasia 6. Nephrotic syndrome (frequently relapsing or steroid-resistant)	1. Kidney transplantation The usual daily dose is 9-12 mg/kg of ciclosporin administered in one or two divided doses orally from the day before transplantation, then decreased by 2 mg/kg per day after that. The usual maintenance dose is 4-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 2. Liver transplantation The usual daily dose is 14-16 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 5-10 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 3. Heart, lung, and pancreas transplantation The usual daily dose is 10-15 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 2-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients.

			4. Bone marrow transplantation The usual daily dose is 6-12 mg/kg of ciclosporin administered in one or two divided doses orally from the day before transplantation. The dose should be maintained for 3-6 months before it gradually decreased and discontinued. 5. Behcet's disease The usual daily dose starts 5 mg/kg of ciclosporin administered in one or two divided doses orally, then decreased or increased by 1-2 mg/kg/day monthly after that. The usual maintenance dose is 3-5 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 6. Psoriasis The usual daily dose is 5 mg/kg administered in two divided doses orally. If improvement is observed, the dose is decreased by 1 mg/kg/day monthly after that. The usual maintenance dose is 3 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 7. Aplastic anaemia The usual daily dose is 6 mg/kg of ciclosporin administered in two divided doses orally. The dose may be adjusted depending on the symptoms of the patients. The treatment effects observed may be larger in patients with shorter duration of illness. It is preferable this drug to be administered to patients with the duration of illness less than 6 months as a

			rule. 8. Nephrotic syndrome The usual daily dose of ciclosporin administered in two divided doses orally is as mentioned below. The dose may be adjusted depending on the symptoms of the patients. (1) Frequently relapsing cases For adult dose, 1.5 mg/kg is administered daily. For child dose, 2.5 mg/kg is administered daily. (2) Steroid-resistant cases For adult dose, 3 mg/kg is administered daily. For child dose, 5 mg/kg is administered daily.
Neoral Oral Solution 10%, Neoral Capsules 10 mg, 25 mg, 50 mg, and others	Novartis Pharma K. K. and others	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, pancreas, and small intestine transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation 3. Behcet's disease (involving ocular complications), and other non-infectious uveitis (limited to active intermediate, posterior non-infectious uveitis that have the risk of causing reduced visual acuity and have not sufficiently responded to conventional treatments) 4. Vulgar psoriasis (refractory or affecting more than 30% of the skin surface), pustular psoriasis, erythrodermic psoriasis, arthropathic psoriasis	1. Kidney transplantation The usual daily dose is 9-12 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation, then decreased by 2 mg/kg per day after that. The usual maintenance dose is 4-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 2. Liver transplantation The usual daily dose is 14-16 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 5 - 10 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 3. Heart, lung, and pancreas transplantation

		5. Aplastic anaemia (severe), pure red cell aplasia 6. Nephrotic syndrome (frequently relapsing or steroid-resistant) 7. Systemic myasthenia gravis (in thymectomized patients in whom steroids are not sufficiently effective or inappropriate due to adverse events 8. Atopic dermatitis (for which conventional therapy is not sufficiently effective or inappropriate)	The usual daily dose is 10-15 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose is gradually decreased after that. The usual maintenance dose is 2-6 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 4. Small intestine transplantation The usual daily dose is 14-16 mg/kg of ciclosporin administered in two divided doses orally. The dose is gradually decreased after that. The usual maintenance dose is 5-10 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. Administration of ciclosporin for injection usually starts from the day before transplantation. Patients should be switched to oral administration as soon as possible. 5. Bone marrow transplantation The usual daily dose is 6-12 mg/kg of ciclosporin administered in two divided doses orally from the day before transplantation. The dose should be maintained for 3 - 6 months before it gradually decreased and discontinued. 6. Behcet's disease and other non-infectious uveitis The usual daily dose starts 5 mg/kg of ciclosporin administered in two divided doses orally, then decreased or increased by 1-2 mg/kg/day monthly after that. The usual maintenance dose is 3-5

			mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 7. Psoriasis The usual daily dose is 5 mg/kg administered in two divided doses orally. If improvement is observed, the dose is decreased by 1 mg/kg/day monthly after that. The usual maintenance dose is 3 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 8. Aplastic anaemia The usual daily dose is 6 mg/kg administered in two divided doses orally. The dose may be adjusted depending on the symptoms of the patients. 9. Nephrotic syndrome The usual daily dose of ciclosporin administered in two divided doses orally is as mentioned below. The dose may be adjusted depending on the symptoms of the patients. (1) Frequently relapsing cases For adult dose, 1.5 mg/kg is administered daily. For child dose, 2.5 mg/kg is administered daily. (2) Steroid-resistant cases For adult dose, 3 mg/kg is administered daily. For child dose, 5 mg/kg is administered daily. 10. Systemic myasthenia gravis The usual daily dose is 5 mg/kg administered in two

			divided doses orally. If improvement is observed, the dose is gradually decreased. The usual maintenance dose is 3 mg/kg daily, but the dose may be adjusted depending on the symptoms of the patients. 11. Atopic dermatitis The usual daily dose for adults is 3 mg/kg administered in two divided doses orally. The dose may be adjusted depending on the symptoms of the patients. The daily dose should not exceed 5 mg/kg.
Papilock Mini Ophthalmic Solution 0.1%	Santen Pharmaceutical Co., Ltd.	Spring catarrh (vernal keratoconjunctivitis, for cases not adequately responsive to antiallergic agent)	Usually one drop 3 times daily to be applied to the affected eye(s).