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Report on Investigation Results

June 15, 2018
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Tacrolimus hydrate
[Branded name]	Prograf Capsules 0.5 mg, and the others (See Appendix)
[Approval holder]	Astellas Pharma Inc., 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

Teratogenicity and fetal toxicity were observed as a result of animal reproductive toxicity studies of rabbits administered tacrolimus hydrate conducted at the time of the initial application for marketing authorization for this drug. Administration of this drug to “pregnant women or women who may be pregnant" is contraindicated according to the current package insert for all the dosage forms or oral and injectable forms, ointment, and ophthalmic solutions specifically.

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 tacrolimus hydrate 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. The Working Group

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 tacrolimus hydrate 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 package insert of tacrolimus hydrate.

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).

Ⅲ. PMDA Investigation

The Working Group, taking into account the latest knowledge and the current medical

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environment, concluded in its report that revision of the package insert is appropriate for preparations containing tacrolimus hydrate, as follows:

1. Contraindication of administration to “pregnant women or women who may be pregnant” in the current package insert

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 Use during Pregnancy, Delivery, or Breastfeeding 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 of tacrolimus hydrate, information should be provided to aid prescribers in their determination of the risks associated with the administration of this drug in the Use during Pregnancy, Delivery, or Breastfeeding section. Specifically, in addition to the results of the aforementioned animal studies, it is appropriate to add statements that the drug is transferred across the placenta in humans and that cases of premature birth or low birth weight baby, and cases involving delivery of neonates exhibiting congenital anomalies by women following organ transplantation have been reported. It is also appropriate that these statements be accompanied with the language concerning the reports of cases of hyperkalaemia and renal impairment that developed in “the neonates delivered by women who received this drug during pregnancy” as included in the overseas package inserts.

Regarding the ointment and ophthalmic solution formulations of tacrolimus hydrate, adding only information concerning the characteristic transfer of this drug across the placenta in humans to the Use during Pregnancy, Delivery, or Breastfeeding section together with the results of relevant animal studies should be sufficient. Whereas, it is not considered appropriate to include the aforementioned information regarding the women following organ transplant or reports on the adverse events that developed in the neonates born from such women. This decision is based on the fact that the ointment and ophthalmic solution of this drug are topical agents and blood concentrations of the drug observed following administration to humans are lower compared with the oral and injectable dosage forms. High blood concentrations may be observed but are generally transient and do not persist. Consequently, although specific blood concentration levels that can affect the neonates are not clear, it is not likely that such topical agents will pose higher risks compared with the oral and injectable dosage forms. The indications of the ointment and ophthalmic solution formulations of this drug was also taking into consideration in the decision.

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.

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] Tacrolimus hydrate (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)-(3) (snip) (4) Pregnant women or women who may be pregnant (Refer to the Use during Pregnancy, Delivery or Breastfeeding section.)	[Contraindications (This drug should not be administered to the following patients)] (1)-(3) (snip) (deleted)
[Precautions] 6. Use during Pregnancy, Delivery or Breastfeeding (1) Pregnant women etc.: This drug should not be administered to pregnant women or women who may be pregnant. [Teratogenic effects and fetal toxicity have been reported in the reproductive toxicity studies using rabbits[3)].] (2) (snip)	[Precautions] 6. Use during Pregnancy, Delivery or Breastfeeding (1) Pregnant women etc.: 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 and fetal toxicity have been reported in the reproductive toxicity studies using rabbits[3)]. Placental transfer in humans has been reported[4)]. Premature birth and influence on the infants (low birth weight, congenital anomalies, hyperkalaemia, renal impairment) have been reported in women who received this drug during pregnancy[5), 6)].] (2) (snip)

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(References) 1)-3) (snip) (newly added) 26) Jain A. et al.:Transplantation 64 (4):559, 1997 4)-25) (snip) 27)-97) (snip)	(References) 1)-3) (snip) 4) Zheng S et al. : Br J Clin Pharmacol 76 (6):988, 2013 5) Coscia LA et al. :Best Pract Res Clin Obstet Gynaecol 28 (8):1174, 2014 26) Jain A. et al. :Transplantation 64 (4):559, 1997 7)-28) (snip) 29)-99) (snip)

*The numbers of literature listed as Reference for this proposed revision correspond to the numbers in the package insert of Prograf Capsules 0.5 mg and 1 mg.

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[Proposed revision] Tacrolimus hydrate (ointment)

Revised language is underlined

Current version	Proposed revision
[Contraindications (This drug should not be administered in the following circumstances)] (1)-(3) (snip) (4) Pregnant women or women who may be pregnant (Refer to the Use during Pregnancy, Delivery, or Breastfeeding section.) (5)-(7) (snip)	[Contraindications (This drug should not be administered in the following circumstances)] (1)-(3) (snip) (deleted) (4)-(6) (snip)
[Precautions] 6. Use during Pregnancy, Delivery, or Breastfeeding (1) Pregnant women etc.: This drug should not be administered to pregnant women or women who may be pregnant. [Teratogenic effects and fetal toxicity have been reported as observed in animal studies (rabbits, orally administered)] (2) (snip)	[Precautions] 6. Use during Pregnancy, Deliver, or Breastfeeding (1) Pregnant women etc.: 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 and fetal toxicity have been reported as observed in animal studies (rabbits, orally administered)[1)]. Placental transfer in humans (orally administered) has been reported[2)].] (2) (snip)

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(References) (newly added) 1)-14) (snip)	(References) 1) Saegusa, T. et al. :The Clinical Report 26 (3):969, 1992 2) Zheng S et al. :Br J Clin Pharmacol 76 (6):988, 2013 1)-16) (snip)

*The section number of the Use during Pregnancy, Delivery or Breastfeeding section and numbers of literature listed as Reference are consistent with the numbers in the package insert of Protopic Ointment 0.1%.

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[Proposed revision] Tacrolimus hydrate (ophthalmic solution)

Revised language is underlined

Current version	Proposed revision
[Contraindications (This drug should not be administered to the following patients)] (1)-(2) (snip) (3) Pregnant women or women who may be pregnant (Refer to the Use during Pregnancy, Delivery, or Breastfeeding section.)	[Contraindications (This drug should not be administered to the following patients)] (1)-(2) (snip) (deleted)
[Precautions] 4. Use during Pregnancy, Delivery, or Breastfeeding (1) This drug should not be administered to pregnant women or women who may be pregnant.(Safety in pregnant women has not been established). [Teratogenic effects and fetal toxicity have been reported as observed in animal studies (rabbits, orally administered)] (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. [Teratogenic effects and fetal toxicity have been reported as observed in animal studies (rabbits, orally administered)[1)]. Placental transfer in humans (orally administered) has been reported[2)].] (2) (snip)

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(References) (Newly added) 1)-7) (snip)	(References) 1) Saegusa, T. et al.:The Clinical Report 26 (3):969, 1992 2) Zheng S et al.:Br J Clin Pharmacol 76 (6):988, 2013 3)-9) (snip)

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Appendix

List of drugs investigated

As of June 2018

Branded name	Marketing authorization holder	Indications	Dosage and administration
Prograf Capsules 0.5 mg, 1 mg, and the others	Astellas Pharma Inc., 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. Myasthenia gravis 4. Rheumatoid arthritis (limited to the cases in which conventional therapy is not sufficiently effective) 5. Lupus nephritis (for which steroids are not sufficiently effective or inappropriate due to adverse reactions) 6. Refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate-to-severe cases) 7. Interstitial pneumonia associated with polymyositis or dermatomyositis	Kidney transplantation The usual dose is 0.15 mg/kg of tacrolimus twice a day orally from 2 days before transplantation. The initial dose after surgery is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.06 mg/kg twice a day orally, but the dose may be adjusted depending on the symptoms of the patients. Liver transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.10 mg/kg, but the dose may be adjusted depending on the symptoms of the patients. Heart transplantation The usual initial dose is 0.03-0.15 mg/kg of tacrolimus twice a day orally. When the drug is administered after an occurrence of rejection, the usual dose is 0.075-0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. After the patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose.

Branded name	Marketing authorization holder	Indications	Dosage and administration
			Lung transplantation The usual initial dose is 0.05-0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. After patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose. Pancreas transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that, gradually decrease the dose and maintain to the minimum effective dose. Small intestine transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that, gradually decrease the dose and maintain to the minimum effective dose. Bone marrow transplantation The usual dose is 0.06 mg/kg of tacrolimus twice a day orally from the day before transplantation. The initial dose after transplantation is 0.06 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. When the drug is administered after an occurrence of graft versus host disease, the usual dose is 0.15 mg/kg of tacrolimus twice a day orally. The dose may be

Branded name	Marketing authorization holder	Indications	Dosage and administration
			adjusted depending on the symptoms of the patients. The absorption of this drug is not constant and can vary depending on individuals when administered orally. The dose should be adjusted based on trough level by measuring blood concentration according to the patient's condition in order to avoid adverse reactions when blood concentration of this drug is high, and occurrence of rejection or graft versus host disease when blood concentration of this drug is low. It is preferable to measure blood concentration frequently especially soon after transplantation and start administration of this drug. When trough concentration exceeds 20 mg/mL for a long period, adverse reactions occur more readily so caution should be exercised. Myasthenia gravis The usual daily dose for adults is 3 mg of tacrolimus once a day administered orally after dinner. Rheumatoid arthritis The usual daily dose for adults is 3 mg of tacrolimus once a day administered orally after dinner. For elderly, start from 1.5 mg once a day

Branded name	Marketing authorization holder	Indications	Dosage and administration
			administered orally after dinner, and the dose may be increased to 3 mg once a day depending on the symptoms of the patients. Lupus nephritis The usual daily dose for adults is 3 mg of tacrolimus once a day administered orally after dinner. Ulcerative colitis Usually the initial daily dose for adults is 0.025 mg/kg of tacrolimus twice a day administered orally after breakfast and dinner. The target trough concentration is 10-15 ng/mL for the next 2 weeks and the dose should be adjusted by monitoring it. The target trough concentration is 5 to 10 ng/mL two weeks after starting the administration and adjust the dose. Interstitial pneumonia associated with polymyositis or dermatomyositis Usually the initial daily dose for adults is 0.0375 mg/kg of tacrolimus twice a day administered orally after breakfast and dinner. The target trough concentration is 5-10 ng/mL after that and the dose should be adjusted by monitoring it.
Prograf Capsules 5 mg, and others	Astellas Pharma Inc.,	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, pancreas, and small	Kidney transplantation The usual dose is 0.15 mg/kg of tacrolimus twice a

Branded name	Marketing authorization holder	Indications	Dosage and administration
	and others	intestine transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation 3. Refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate-to-severe cases)	day orally from 2 days before transplantation. The initial dose after surgery is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.06 mg/kg twice a day orally, but the dose may be adjusted depending on the symptoms of the patients. Liver transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.10 mg/kg, but the dose may be adjusted depending on the symptoms of the patients. Heart transplantation The usual initial dose is 0.03-0.15 mg/kg of tacrolimus twice a day orally. When the drug is administered after an occurrence of rejection, the usual dose is 0.075-0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. After patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose. Lung transplantation The usual initial dose is 0.05-0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the

Branded name	Marketing authorization holder	Indications	Dosage and administration
			patients. After patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose. Pancreas transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that gradually decrease the dose and maintain to the minimum effective dose. Small intestine transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that gradually decrease the dose and maintain to the minimum effective dose. Bone marrow transplantation The usual dose is 0.06 mg/kg of tacrolimus twice a day orally from the day before transplantation. The initial dose after transplantation is 0.06 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. When the drug is administered after an occurrence of graft versus host disease, the usual dose is 0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. The absorption of this drug is not constant and

Branded name	Marketing authorization holder	Indications	Dosage and administration
			varies depending on individuals when administered orally. The dose should be adjusted based on trough level by measuring blood concentration according to the patient's condition in order to avoid adverse reactions when blood concentration of this drug is high, and occurrence of rejection or graft versus host disease when blood concentration of this drug is low. It is preferable to measure blood concentration frequently especially soon after transplantation and start administration of this drug. When trough concentration exceeds 20 mg/mL for a long period, adverse reactions occur more readily so caution should be exercised. Ulcerative colitis Usually the initial daily dose for adults is 0.025 mg/kg of tacrolimus twice a day administered orally after breakfast and dinner. The target trough concentration is 10 - 15 ng/mL for the next 2 weeks and the dose should be adjusted by monitoring it. The target trough concentration is 5 to 10 ng/mL two weeks after starting the administration and adjust the dose.
Prograf Injection 2 mg, 5 mg	Astellas Pharma Inc.	1. Prophylaxis of organ rejection in kidney, liver, heart, lung, pancreas, and small	Kidney transplantation The usual dosage is 0.10 mg/kg of tacrolimus

Branded name	Marketing authorization holder	Indications	Dosage and administration
		intestine transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation	diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible. Liver transplantation The usual dosage is 0.10 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible. Heart transplantation The usual dosage is 0.05 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible. Lung transplantation The usual dosage is 0.05 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible. Pancreas transplantation The usual dosage is 0.10 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24

Branded name	Marketing authorization holder	Indications	Dosage and administration
			hours. Patients should be switched to oral administration as soon as possible. Small intestine transplantation The usual dosage is 0.10 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible. Bone marrow transplantation The usual dosage is 0.03 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours from the day before transplantation. When the drug is administered after an occurrence of graft versus host disease, the usual dosage is 0.10 mg/kg of tacrolimus diluted with normal saline or glucose injection, and administered as an intravenous infusion over 24 hours. Patients should be switched to oral administration as soon as possible The blood concentration of this drug varies depending on individuals. The dose should be adjusted by measuring blood concentration according to the patient’s condition in order to avoid adverse reactions when blood concentration

Branded name	Marketing authorization holder	Indications	Dosage and administration
			of this drug is high, and occurrence of rejection or graft versus host disease when blood concentration of this drug is low. It is preferable to measure blood concentration frequently especially soon after transplantation and start administration of this drug.
Prograf Granules 0.2 mg, 1 mg	Astellas Pharma Inc.	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. Myasthenia gravis	Kidney transplantation The usual dose is 0.15 mg/kg of tacrolimus twice a day orally from 2 days before transplantation. The initial dose after surgery is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.06 mg/kg twice a day orally, but the dose may be adjusted depending on the symptoms of the patients. Liver transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally, then is gradually decreased after that. The usual maintenance dose is 0.10 mg/kg, but the dose may be adjusted depending on the symptoms of the patients. Heart transplantation The usual initial dose is 0.03-0.15 mg/kg of tacrolimus twice a day orally. When the drug is administered after an occurrence of rejection, the

Branded name	Marketing authorization holder	Indications	Dosage and administration
			usual dose is 0.075 - 0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. After patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose. Lung transplantation The usual initial dose is 0.05-0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. After patient is stabilized, gradually decrease the dose and maintain to the minimum effective dose. Pancreas transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that gradually decrease the dose and maintain to the minimum effective dose. Small intestine transplantation The usual initial dose is 0.15 mg/kg of tacrolimus twice a day orally. After that gradually decrease the dose and maintain to the minimum effective dose. Bone marrow transplantation The usual dose is 0.06 mg/kg of tacrolimus twice a day orally from the day before transplantation. The initial dose after transplantation is 0.06 mg/kg of

Branded name	Marketing authorization holder	Indications	Dosage and administration
			tacrolimus twice a day orally, then is gradually decreased after that. When the drug is administered after an occurrence of graft versus host disease, the usual dose is 0.15 mg/kg of tacrolimus twice a day orally. The dose may be adjusted depending on the symptoms of the patients. The absorption of this drug is not constant and varies depending on individuals when administered orally. The dose should be adjusted based on trough level by measuring blood concentration according to the patient's condition in order to avoid adverse reactions when blood concentration of this drug is high, and occurrence of rejection or graft versus host disease when blood concentration of this drug is low. It is preferable to measure blood concentration frequently especially soon after transplantation and start administration of this drug. When trough concentration exceeds 20 mg/mL for a long period, adverse reactions occur more readily so caution should be exercised. Myasthenia gravis The usual daily dose for adults is 3 mg of

Branded name	Marketing authorization holder	Indications	Dosage and administration
			tacrolimus once a day administered orally after dinner.
Graceptor Capsules 0.5 mg, 1 mg, 5 mg	Astellas Pharma Inc.	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	Kidney transplantation The usual dose is 0.15-0.20 mg/kg of tacrolimus administered orally once a day in morning from 2 days before transplantation. The dose may be adjusted depending on the symptoms of the patients. Liver transplantation Usually the initial dose after surgery is 0.10-0.15 mg/kg of tacrolimus once a day administered orally in morning. The dose may be adjusted depending on the symptoms of the patients. When switching from Prograf oral drug (transplantation of kidney, liver, heart, lung, pancreas, small intestine, and bone marrow) Usually when switching from Prograf oral drug, administer the same daily dose orally once a day in morning. The absorption of this drug is not constant and varies depending on individuals when administered orally. The dose should be adjusted based on trough level by measuring blood concentration according to the patient’s condition

Branded name	Marketing authorization holder	Indications	Dosage and administration
			in order to avoid adverse reactions during high blood concentrations of this drug, and occurrence of rejection or graft versus host disease when blood concentration of this drug is low. It is preferable to measure blood concentration frequently especially soon after transplantation and start administration of this drug. When trough concentration exceeds 20 mg/mL for a long period, adverse reactions occur more readily so caution should be exercised.
Protopic Ointment 0.1%, and the others	Maruho Co., Ltd., and others	Atopic dermatitis	For adult dose, usually once or twice daily to be applied to the affected area. The amount per application should not exceed 5g.
Protopic Ointment 0.03% for Pediatric	Maruho Co., Ltd.	Atopic dermatitis	For child dose, usually once or twice daily to be applied to the affected area. The amount per application should not exceed 5g, but it may be adjusted depending on the age of the patients.
Talymus Ophthalmic Suspension 0.1%	Senju Pharmaceutical Co., Ltd.	Spring catarrh (vernal keratoconjunctivitis, for cases not adequately responsive to antiallergic agent)	Mix well when use. Usually one drop 2 times daily to be applied to the affected eye(s).