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**Revised: July 2018 (8th version)
*Revised: March 2018

Standard Commodity Classification No. of Japan	871319

Storage: Store at room temperature.
Shelf life: Three years from manufacturing date (even prior to the expiration date, use as soon as possible after first opening the bottle cap).

Approval No.	22000AMX00017
Date of listing in the NHI reimbursement price	April 2008
Date of initial marketing in Japan	May 2008
International birth date	April 1993

Vernal conjunctivitis agent

Powerful drug
Prescription-only drug[Note)]

TALYMUS ® OPHTHALMIC SUSPENSION 0.1%

Tacrolimus hydrate ophthalmic suspension

Note) Caution – Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (This drug is contraindicated to the following patients)
(1) Patients with a history of hypersensitivity to any of the ingredients of this product
(2) Patients with eye infection
[The infection may worsen due to the immunosuppressive effect of TALYMUS OPHTHALMIC SUSPENSION 0.1%]

COMPOSITION AND PRODUCT DECRIPTION

Active ingredient/content (per 1 mL)	Tacrolimus hydrate 1.02 mg (1 mg as tacrolimus)
Inactive ingredients	Partially hydrolyzed polyvinyl alcohol, Benzalkonium chloride, Sodium chloride, Dibasic sodium phosphate hydrate, Sodium dihydrogen phosphate dihydrate, Phosphoric acid, Sodium hydroxide
Dosage form	Aqueous ophthalmic suspension
Color	White
pH	4.3 to 5.5
Osmotic pressure ratio	Ratio to physiological saline: 0.9–1.1
Other	Sterile preparation

INDICATIONS
Vernal conjunctivitis (in patients with inadequate response to anti-allergic agents)

PRECAUTIONS CONCERNING INDICATIONS
TALYMUS OPHTHALMIC SUSPENSION 0.1% may be used only in patients noted as having the growth of giant papillae on the palpebral conjunctiva judged to inadequately respond to anti-allergic agents.

DOSAGE AND ADMINISTRATION
Usually, instill 1 drop in the eye twice daily after shaking it well to mix.

PRECAUTIONS**
1. Important Precautions
(1) TALYMUS OPHTHALMIC SUSPENSION 0.1% should be used under the supervision of a physician well experienced in treating vernal conjunctivitis.
(2) Infection may occur or worsen during treatment with TALYMUS OPHTHALMIC SUSPENSION 0.1%, and the risk of infection may increase during concomitant use with another drug with immunosuppressive effect, which requires adequate caution.
(3) Patients should be informed that burning sensation in eye, eye irritation, etc. have been frequently observed after use of TALYMUS OPHTHALMIC SUSPENSION 0.1%.
(4) Prolonged use of TALYMUS OPHTHALMIC SUSPENSION 0.1% requires close monitoring, and careless continuation of treatment should be avoided. When any abnormality is noted, appropriate measures should be taken, such as discontinuation of the treatment.
(5) In glaucoma patients, the use of TALYMUS OPHTHALMIC SUSPENSION 0.1% may cause increase in intraocular pressure, and thus requires periodic measurement of intraocular pressure during the treatment.

2. Adverse Reactions
Adverse reactions were reported in 55 of 86 patients (64.0%) treated in clinical studies conducted by the time of approval. Major adverse reactions were abnormal sensation in eye (burning sensation in eye, foreign body sensation in eyes, eye strange sensation of) in 38 patients (44.2%), eye irritation in 18 patients (20.9%), and lacrimation increased in 10 patients (11.6%) (data at the time of approval).

	≥5%	≥0.1, <5%	Incidence unknown
Hypersensitivity [Note)]			Contact dermatitis
Eye [Note)]	(≥40%) Abnormal sensation in eye (burning sensation in eye, foreign body sensation in eyes, eye strange sensation of) (≥20%, <40%) Eye irritation (≥10%, <20%) Lacrimation increased	Asthenopia, dry eye, eye discharge, eye pain, ocular hyperaemia, photophobia, punctate keratitis	Eye pruritus, ocular discomfort, feeling of heaviness in the upper eyelids, eyelid pruritus, eyelid oedema, blepharitis, chalazion, meibomianitis, conjunctival hyperaemia, conjunctival oedema, conjunctivitis, conjunctival erosion, conjunctival deposit, corneal erosion, corneal

	≥5%	≥0.1, <5%	Incidence unknown
			ulcer, corneal opacity, anterior chamber flare, anterior chamber cell, synchysis scintillans, vision blurred, visual acuity reduced, glaucoma aggravated, intraocular pressure increased
Respiratory Note)		Throat irritation, pharyngolaryngeal pain, pharyngeal hypoaesthesia	Nasal discomfort
Infection Note)		Keratitis herpetic, herpes eyelid	Impetigo, hordeolum, conjunctivitis bacterial, herpes simplex virus conjunctivitis, epidemic keratoconjunctivitis, keratitis bacterial
Other Note)		Feeling hot [in face], neutrophils decreased, monocytes increased	Numbness of fingers, AST (GOT) increased, gamma-GTP increased, LDH increased, white blood cell count increased, white blood cell count decreased, neutrophils increased, lymphocytes decreased, blood uric acid increased

The adverse reactions listed above are based on the results of twice-daily instillation of the 0.1 formulation (this product), except for the "Incidence unknown" column in which the listed adverse reactions are based on the results of studies using other formulations or dosage regimens (i.e., 0.01% formulation, 0.03% formulation, or more than twice-daily instillation) including a long-term dose study for a maximum of 5 years and drug use investigation.

Note: When any of these adverse reactions is noted, appropriate measures should be taken, such as discontinuation of the treatment.

3. Geriatric Use

Since elderly patients generally have decreased physiological function, caution should be exercised.

4. Use during Pregnancy, Delivery, or Lactation

**(1) In pregnant women or women suspected of being pregnant, this product may only be used when the expected therapeutic benefit outweighs the possible risks of treatment. [Animal studies (in rabbits, oral administration) reported teratogenicity and fetotoxicity of tacrolimus.[1)] In humans (oral administration), transplacental transfer of tacrolimus has been reproted.[2)]]

(2) Nursing mothers should be instructed to discontinue breast feeding during the treatment. [Tacrolimus may be transferred into breast milk.]

5. Pediatric Use

The safety of this product has not been established in low birth-weight infants, neonates, nursing infants, or young children aged younger than 6 years (no experience of use).

6. Precautions concerning Use

(1) Route of administration: Instillation into the eye only.

(2) At administration:

1) Patients should be instructed to compress the lacrimal sac area while closing the eye for 1 to 5 minutes after instillation.
2) Patients should be instructed to promptly wipe off any excess medicine on the eyelid skin, etc. after instillation.
3) At instillation, caution should be taken to avoid touching the tip of the container directly against the eye.
4) When any other ophthalmic solution is concomitantly used, at least a 5-minute interval should be allowed between different drugs.
5) Benzalkonium chloride may be absorbed by contact lenses. Patients wearing contact lenses should remove them before instillation and wait for a sufficient time before reinserting them.

(3) At dispensing: At the time of dispensing this drug, patients should be instructed not to remove the film from the body of the container (excluding the film over the cap) [because the light-resistant film maintains the quality of the product].

PHARMACOKINETICS

Blood Level

1. After single instillation of TALYMUS OPHTHALMIC SUSPENSION 0.1% one drop in one eye in 7 healthy adult male subjects, tacrolimus was detected in blood in all subjects. The C_{max} was 0.086 to 0.23 ng/mL and the t_{max} was 1 or 3 hours.

Table 1 Tacrolimus Concentration in Whole Blood after a Single Instillation

Subject No.	Tacrolimus concentration in whole blood (ng/mL)							
	Time after instillation (h)							
	0	0.5	1	3	6	9	12	24
1	nd	nd	0.11	0.23	0.076	0.071	0.075	nd
2	nd	nd	0.051	0.094	nd	nd	nd	nd
3	nd	nd	0.066	0.15	0.080	0.073	0.051	nd
4	nd	nd	0.086	0.084	nd	nd	nd	nd
5	nd	nd	nd	0.13	0.065	nd	nd	nd
7	nd	nd	0.17	0.15	0.078	nd	nd	nd
8	nd	0.057	0.18	0.22	0.097	0.053	nd	nd

nd: Below the limit of quantitation (0.051 ng/mL)

2. After repeated instillations of TALYMUS OPHTHALMIC SUSPENSION 0.1% one drop in both eyes four times daily at 4-hour intervals for 10 days in 7 healthy adult male subjects, the pharmacokinetic parameters calculated from tacrolimus concentrations in whole blood were as shown in Table 2. Since the AUC

and the C_{max} on Day 7 were similar to those on Day 10, the tacrolimus blood concentration appeared to have reached steady-state by Day 7.

Table 2 Pharmacokinetic Parameters during Repeated Instillations

Time point	No. of subjects	Cmax (ng/mL)	tmax† (h)	AUC‡ (ng·h/mL)	t 1/2 (h)
Day 1	7	0.41±0.22	13±5	6.20± 3.57	—
Day 7	7	1.04±0.54	9±4	20.47±10.21	—
Day 10	7	1.15±0.67	11±6	22.49±12.68	35.2±14.9

(Mean ± SD)

†: Time after the first instillation on the day. More specifically, 13, 9, and 11 hours after the first instillation on the day corresponded to 1 hour after the fourth instillation, 1 hour after the third instillation, and 3 hours after the third instillation, respectively.
‡: The AUCs on Days 1, 7, and 10 were specifically $AUC_{0\text{-}23h}$, $AUC_{\text{-}1\text{-}23h}$, $AUC_{\text{-}1\text{-}24h}$, respectively.
Note: For the approved dosage and administration of this drug, see "DOSAGE AND ADMINISTRATION".

3. In patients with vernal conjunctivitis treated with TALYMUS OPHTHALMIC SUSPENSION 0.1% one drop twice daily for 4 weeks, the blood tacrolimus concentrations were as shown in the table below.

Time point	No. of subjects	Tacrolimus concentration in blood (ng/mL)	
		Mean ± SD	Minimum – Maximum
Week 1	2	0.315±0.445	nd to 0.63
Week 2	56	0.219±0.367	nd to 1.34
Week 4	53	0.297±0.446	nd to 1.36

nd: Below the limit of quantitation (0.50 ng/mL)

4. In patients with vernal conjunctivitis treated with TALYMUS OPHTHALMIC SUSPENSION 0.1% one drop twice daily for about 12 weeks (i.e., 70–97 days) (in a post-marketing clinical trial), the blood tacrolimus concentrations were as shown in the table below.

Time point	No. of subjects	Tacrolimus concentration in blood (ng/mL)	
		Mean ± SD	Minimum – Maximum
Week 4	50	0.286±0.485	nd to 1.69
Week 12	51	0.305±0.525	nd to 1.83
End of treatment	51	0.305±0.525	nd to 1.83

nd: Below the limit of quantitation (0.50 ng/mL)

(Reference data)
Blood Level [Adult renal transplant recipients][3)]
In 9 adult renal transplant recipients who received oral administration of tacrolimus capsules at 0.16 mg/kg, the pharmacokinetic parameters were as shown in the table below.

t_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	Trough level* (ng/mL)	F** (%)
4.2±2.9	44±45	274±198	16±12	20±17.8

(Mean ± SD)

*: Blood concentration at 12 hours post-dose
**: Bioavailability

Blood Level [Pediatric hepatic transplant recipients][4)]
In pediatric hepatic transplant recipients (mean age, 5.3 years), the body weight-based oral doses 2.7 to 4.4 times higher than the adult doses yielded similar blood tacrolimus concentrations (data from non-Japanese patients who received administration of tacrolimus capsules).

Blood Level [Adult renal transplant recipients][5)]
In 9 adult renal transplant recipients who received oral administration of tacrolimus capsules and granules at the same doses, the pharmacokinetic parameters were as shown in the table below.

Subject No.	Dose (mg/kg /dose)	Capsules		Granules		Ratio (Granules/Capsules)	
		C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	C_{max}	$AUC_{0\text{-}12h}$
1	0.03	10	42.7	18	94.4	1.80	2.21
2	0.02	10	70.2	9.3	68.6	0.93	0.98
3	0.06	27	165.4	23	113.3	0.85	0.69
4	0.02	14	105.6	7.2	41.8	0.51	0.40
6	0.02	9.9	61.5	14	69.2	1.41	1.13
7	0.03	13	92.0	13	103.8	1.00	1.13
8	0.02	6.2	36.7	6.8	27.6	1.10	0.75
9	0.02	4.1	32.6	3.8	34.1	0.93	1.05
10	0.04	20	230.8	42	320.0	2.10	1.39
Mean ± SD	–	–	–	–	–	1.18± 0.50	1.08±0.51

Note: Adverse reactions are more likely to occur with a longer period of trough tacrolimus blood concentrations exceeding 20 ng/mL.

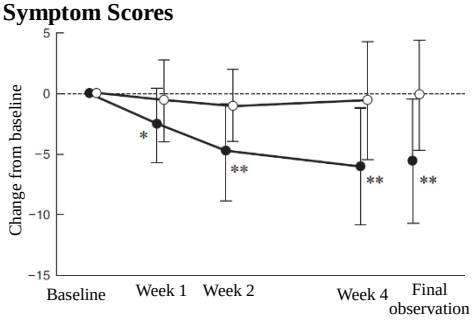
Blood Level [Rabbits]
In rabbits, based on calculation from the whole blood $AUC_{0\text{-}24h}$ after single instillation of TALYMUS OPHTHALMIC SUSPENSION 0.1% in one eye compared with the $AUC_{0\text{-}24h}$ after intravenous administration, the rate of transfer of tacrolimus to the blood after instillation of this drug was 11.1%.

Distribution in eye tissues [Rabbits]
In rabbits given single instillation of tacrolimus ophthalmic formulation 0.1% (this product), 0.3%, or 1.0% one drop in one eye, the ocular tissue tacrolimus concentrations tended to be higher at higher doses, with predominant distribution in the conjunctiva and cornea.
In rabbits given repeated instillations
of tacrolimus ophthalmic formulation 0.3% one drop in one eye 4 times daily at 3-hour intervals for 14 days, the ocular tissue tacrolimus concentrations nearly reached steady-state by Day 7 except for the lens. The lens concentration of tacrolimus reached near steady-state by Month 3 in a separate 6-month repeat-instillation study.

CLINICAL STUDIES
In a double-blind, placebo-controlled, parallel-group comparative study in patients with vernal conjunctivitis (aged ≥6 years) inadequately responding to anti-allergic ophthalmic solutions, TALYMUS OPHTHALMIC SUSPENSION 0.1% significantly improved the total clinical symptom score†, as compared with placebo.[6)]
†: Sum of severity scores for palpebral conjunctival hyperaemia, palpebral conjunctival swelling, palpebral conjunctival follicles, palpebral conjunctival papillae, giant papillae on the palpebral conjunctiva, bulbar conjunctival hyperaemia, bulbar conjunctival oedema, limbal Trantas dots, limbal swelling, and corneal epithelium

Figure Change from Baseline in Total Clinical

Symptom Scores



	(Baseline)	(Week 1)	(Week 2)	(Week 4)	(Final observation)
○ Placebo n=	28,	28,	25,	22,	28
● TALYMUS n=	28,	28,	27,	27,	28

(Final observation: at Week 4 or discontinuation)
*: $p<0.05$
**: $p<0.01$ (two-sample t-test) Mean ± SD

PHARMACOLOGY

1. Pharmacological action[7)]

1) Effect in an experimental rat model of allergic conjunctivitis
In a rat model of ovalbumin-induced delayed-type (type I) allergic conjunctivitis, instillation of tacrolimus ophthalmic formulation suppressed increases in conjunctival eosinophils and T cells.

2) Effect in an experimental rabbit model of allergic conjunctivitis
In a rabbit model of tuberculin-induced delayed-type (type IV) allergic conjunctivitis, instillation of tacrolimus ophthalmic formulation suppressed the onset of conjunctival hyperemia and oedema.

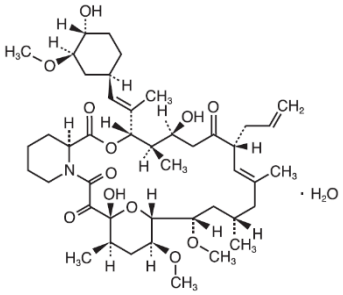
2. Mechanism of action

Tacrolimus has calcineurin-inhibiting effect[8)], with confirmed *in vitro* suppression of the production of cytokines (IL-2, IL-4, IL-5, and IFN-γ) from human peripheral blood mononuclear cells (IC_{50} values: 0.02 to 0.11 ng/mL)[9)].

PHYSICOCHEMICAL PROPERTIES

Nonproprietary name: Tacrolimus Hydrate [JAN]
Chemical name:
(3*S*, 4*R*, 5*S*, 8*R*, 9*E*, 12*S*, 14*S*, 15*R*, 16*S*, 18*R*, 19*R*, 26a*S*)-5, 19-Dihydroxy-3{-(1*E*)-2-[(1R, 3R, 4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl}-14, 16-dimethoxy-4, 10, 12, 18-tetramethyl-8(-prop-2-en-1-yl)-15, 19-epoxy-5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 26, 26a-hexadecahydro-3H-pyrido [2,1-*c*][1,4] oxaazacyclotricosine- 1, 7, 20, 21(4*H*, 23*H*)-tetrone monohydrate

Structural formula:



Molecular formula: $C_{44}H_{69}NO_{12}$・H_2O
Molecular weight: 822.03
Description: Tacrolimus hydrate occurs as white, crystal or crystalline powder. It is very soluble in methanol and in ethanol (99.5), freely soluble in *N*,*N*-dimethylformamide and in ethanol (95), and practically insoluble in water.

PACKAGING

5 mL×1

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9) Sakuma, S. et al.: Int. Immunopharmacol., 1, 1219, 2001.

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