Published by
Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Tacrolimus hydrate (ointment 0.1%)

December 8, 2021

Therapeutic category

Other agents for epidermis

Non-proprietary name

Tacrolimus hydrate

Safety measure

Precautions should be revised in the package insert.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

Current	Revision
Warnings In a dermal carcinogenicity study in mice, an increased incidence of lymphoma due to persistently higher blood concentrations of this drug was observed. Cases of lymphoma or skin cancer have been reported in patients treated with this drug as well, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration.	Warnings (deleted)
Important Precautions (N/A)	Important Precautions The immunosuppressive effects of this drug present a potential risk of carcinogenicity. In the long-term post-marketing survey conducted in Japan with the 0.03% preparation, no cases of malignant lymphoma, skin cancer or other malignant tumor have been reported. No increase in the risk of carcinogenicity associated with this drug was observed either in an overseas long-term epidemiological study. On the other hand, cases of malignant lymphoma or skin cancer have been reported in patients treated with this drug, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration.

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The local immunosuppressive effects (that may result in increased infections or induce skin cancer) of this drug in long-term use of 2 years or more are unknown due to the lack of clinical data on such use.	(deleted)
Other Precautions (N/A)	Other Precautions In order to assess the long-term carcinogenic risk of this drug, an epidemiological study (a prospective cohort study for 10 years) was conducted overseas in pediatric patients with atopic dermatitis. During 44 629 person-years of observation, malignant tumor was reported in 6 cases and the standardized incidence ratio relative to the expected number of 5.95 cases in the sex- and age-matched population was 1.01 (95% CI: 0.37 to 2.20).

(Reference) Paller A.S., et al.: J. Am. Acad. Dermatol. 2020; 83(2):375-381

N/A: Not Applicable. No corresponding language is included in the current package insert.

Revision in line with the Instructions for Electronic Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0611-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 11, 2021 (New instructions): Revised language is underlined.

Current	Revision
1. WARNINGS In a dermal carcinogenicity study in mice, an increased incidence of lymphoma due to persistently higher blood concentrations of this drug was observed. Cases of lymphoma or skin cancer have been reported in patients treated with this drug as well, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration.	1. WARNINGS (deleted)
8. IMPORTANT PRECAUTIONS (N/A)	8. IMPORTANT PRECAUTIONS The immunosuppressive effects of this drug present a potential risk of carcinogenicity. In the long-term post-marketing survey conducted in Japan with the 0.03% preparation, no cases of malignant lymphoma, skin cancer or other malignant tumor have been reported. No increase in the risk of carcinogenicity associated with this drug was observed either in an overseas long-term epidemiological study. On the other hand, cases of lymphoma or skin cancer have been reported in patients treated with this drug, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration.

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The local immunosuppressive effects (that may result in increased infections or induce skin cancer) of this drug in long-term use of 2 years or more are unknown due to the lack of clinical data on such use.	(deleted)
15. OTHER PRECAUTIONS (N/A)	15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Use In order to assess the long-term carcinogenic risk of this drug, an epidemiological study (a prospective cohort study for 10 years) was conducted overseas in pediatric patients with atopic dermatitis. During 44 629 person-years of observation, malignant tumor was reported in 6 cases and the standardized incidence ratio relative to the expected number of 5.95 cases in the sex- and age-matched population was 1.01 (95% CI: 0.37 to 2.20).

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Safety measure

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Current	Revision
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The local immunosuppressive effects (that may result in increased infections or induce skin cancer) of this drug in long-term use of 2 years or more are unknown due to the lack of clinical data on such use.	(deleted)
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