

PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency



No. 12 October 2019

Serious Skin Disorders with Lamotrigine and Adherence to Dosage and Administration

A high incidence of skin disorders has been reported when lamotrigine was administered at higher doses or frequencies than approved dosage and administration. Precautions have been issued through various means including the PMDA Alert for Proper Use of Drugs in January 2012 and the Dear Healthcare Professional Letter of Rapid Safety Communication (Blue Letter) in February 2015.

Dosage and administration of lamotrigine are closely regulated in terms of dosage and dose increase intervals depending on the specific indications and concomitant pharmaceuticals. Please read the package insert (PI) carefully before use or otherwise to keep the following precautions in mind.

◎ Adhere to Dosage and Administration

- **Prescribed starting dose** should not be exceeded.
- **Timing of dose increase** should not be earlier than prescribed.

◎ Provide medication guidance to patients regarding serious skin disorders in line with PI

- Adverse reactions such as **serious skin disorders** may occur.
 - Patients should seek medical attention **immediately when they experience initial symptoms** of skin disorders.
 - **Dosage and Administration must be adhered to.**
- Of the 104 cases of serious skin disorder associated with lamotrigine reported from November 2017 to October 2018, information on the adherence to the dosage and administration was available in 58 cases and 19 of the 58 cases did not adhere to the dosage and administration prescribed.
 - Cases of serious skin disorder are in principle not considered the proper use under the Relief System for Adverse Drug Reactions if medication does not adhere to the dosage and administration prescribed and they are not eligible for relief benefits. There has been no end to cases of patients who file an application for compensation for adverse reactions that they claim occurred following their use of lamotrigine but fail to receive the relief benefit payments because their use are considered improper. Of the 235 non-payment cases due to improper use under the Relief System for Adverse Drug Reactions between 2014 and 2018, 92 cases were administered lamotrigine (Pharmaceuticals and Medical devices Safety Information No. 367)

Serious skin disorder with non-adherent use to Dosage and Administration

Case 1 : Drug-induced hypersensitivity syndrome with lamotrigine started at a dose exceeding specified dosage and administration

A teenage woman prescribed Lamictal Tablets (lamotrigine) for epilepsy in combination with sodium valproate started the treatment at 50 mg every day and developed drug-induced hypersensitivity syndrome.

※ Dosage and administration for epilepsy in combination with sodium valproate :

Usual dose is 25 mg of lamotrigine administered orally on alternate days for Week 1-2, followed by 25 mg/day once daily orally for Week 3-4. For Week 5 or later lamotrigine is gradually increased by 25-50 mg/day every 1 or 2 weeks. The maintenance dose is 100-200 mg/day administered orally twice daily in divided doses.

(Partial edited excerpt from Pharmaceuticals and Medical Devices Information No. 357)

Case 2 : Drug-induced hypersensitivity syndrome with lamotrigine started at a dose exceeding specified dosage and administration and increased earlier than specified

A man in his forties prescribed Lamictal Tablets (lamotrigine) for bipolar affective disorder without sodium valproate and with drugs other than those inducing glucuronidation started the treatment at 50 mg/day every day, increased the dose to 100 mg/day after 7 days, then to 150 mg/day after 14 days, and to 200 mg/day after 21 days of administration and developed drug-induced hypersensitivity syndrome.

※ Dosage and administration for suppression of recurrent/relapsed mood episode in patients with bipolar disorder without sodium valproate and with drugs other than those inducing glucuronidation :

Usual adult dose is 25 mg/day of lamotrigine administered orally once daily or twice daily in divided doses for Week 1-2, followed by 50mg/day once daily or twice daily in divided doses for Week 3-4 then 100 mg/day for Week 5. 200mg/day is administered orally once daily or twice daily in divided doses for Week 6 and later as maintenance dose. Dose should be titrated appropriately depending on the patient's conditions in Week 6 or later by ≤ 100 mg/day at an interval of 1 week or longer within 400 mg of daily dose administered orally once daily or twice daily in divided doses.

(Partial edited excerpt from Pharmaceuticals and Medical devices Information No. 357)

Please also refer to the Manuals for Management of Individual Serious Adverse Drug Reactions for early detection and treatment of serious skin disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) (only in Japanese)

(<https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html>)

About this information

- * PMDA Alert for Proper Use of Drugs communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the PMD Act.
- * We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future
- * This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided to promote the proper use of the drugs.

Access to the most up to date safety information is available via the PMDA medi-navi

