PMDA Alert for Proper Use of Drugs

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*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail*

# Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine)-induced Serious Skin Disorders

**A high incidence of skin disorders has been reported in cases where administration of Lamictal Tablets was not in compliance with the "Dosage and Administration" section** (See Table 1). Healthcare professionals have been alerted to comply with the authorized dosage since the time of new drug approval in October 2008.
However, 397 cases of serious skin disorders, such as Stevens-Johnson syndrome, were reported between December 2008 and November 2011. **Of the 251 cases where the information on the dosage of Lamictal Tablets was available, 152 cases (approximately 60%) involved noncompliance with the authorized dosage** (See Table 2).

## Thoroughly comply with "Dosage and Administration."

- **The maximum daily dose should not be exceeded.**
- **Dose increase should not be attempted earlier than the specified timing.**
- **When using lamotrigine with sodium valproate (VPA), the treatment should be given every other day rather than everyday for the first 2 weeks (in adults only).**

## Ensure patients are given medication instructions about possible serious skin disorders.

- **Adverse reactions such as serious skin disorders may occur.**
- **The patient should see his/her doctor immediately if he/she has any initial symptoms of a serious skin disorder.**
- **The dosage and administration should be adhered to.**

<Initial symptoms>
Ocular hyperaemia, pharynx pain, sore lips/oral sore, pyrexia (≥38°C), general malaise, rash, etc.

## Table 1 Incidence of skin disorders reported in Japanese clinical trial (in concomitant with VPA)

| | Dose exceeding the authorized dose | Authorized dose[Note 1] |
|---|---|---|
| Incidence of skin disorders[Note 2] | 10.4% (18/173)<br>including 5 serious cases | 2.9% (3/102)<br>including 1 serious case |

Note 1) See the package insert or Table 3 for the authorized dosage of Lamictal Tablets.
Note 2) All reported cases of rash, including enanthema (incidence = number of cases/number of cases analyzed)

## Table 2 Noncompliance/compliance with the authorized dosage among the cases of serious skin disorders reported after the initial marketing

| | Noncompliance with the authorized dose[Note 1]<br>(152 cases; 160 events) | Compliance with the authorized dose<br>(99 cases, 113 events) |
|---|---|---|
| Noncompliance/compliance with the "Dosage and Administration"[Note 2]<br>(Number of major events[Note 3]) | 60.6% (152/251)<br>Toxic epidermal necrosis (9 events)<br>Stevens-Johnson syndrome (33 events)<br>Hypersensitivity syndrome (27 events) | 39.4% (99/251)<br>Toxic epidermal necrosis (2 events)<br>Stevens-Johnson syndrome (20 events)<br>Hypersensitivity syndrome (8 events) |

Note 1) See the package insert or Table 3 for the authorized dosage of Lamictal Tablets.
Note 2) Data from 251 of 397 cases of serious skin disorders reported between December 2008 and November 2011 where the information on the dosage of Lamictal Tablets was available.
Note 3) Patients with multiple events are included.

## Cases of a serious skin disorder (Stevens-Johnson syndrome)

### Case 1

A female patient in her 30s.
The patient has been receiving VAP for the treatment of epilepsy. Administration of Lamictal Tablets 25 mg was started on alternate days. The dose of Lamictal Tablets was increased to 25 mg/day on Day 15 and to 50 mg/day 7 days later (Day 22). On Day 36, the patient had generalized pruritus and hot feeling. Administration of Lamictal Tablets was discontinued on the following day. One day after discontinuation, the patient visited the dermatology department and was admitted to the hospital for suspected drug eruption. Steroid pulse therapy (drip infusion of methylprednisolone 500 mg/day) was performed. The drug eruption gradually remitted, and the patient was discharged from the hospital 16 days after discontinuation of Lamictal Tablets.

### Case 2

A female patient in her 20s.
The patient has been receiving VPA, lithium carbonate and other medications for the treatment of bipolar II disorder. Administration of Lamictal Tablets 12.5 mg/day was started. On Day 10, the dose of Lamictal Tablets was increased to 25 mg/day. On Day 16, the patient started to have red eyes. On Day 17, the lips became swollen and numb. The patient visited an emergency hospital. Ophthalmic medication and antibiotics were prescribed for suspected bacterial infection. On Day 20, the patient visited Hospital A (general medicine) and bacterial infection was suspected. On Day 21, after visiting Hospital B (internal medicine), the patient visited the internal medicine department at Hospital C. After that, the patient visited the dermatology department at Hospital C. The patient was found to have Stevens-Johnson syndrome, and she was admitted to the hospital. After admission, steroid therapy was started. On Day 36, Stevens-Johnson syndrome remitted. The patient was discharged from the Hospital C.

## Lamotrigine package insert (excerpt)

**[WARNINGS]**

**Serious skin disorders such as Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrosis (Lyell syndrome) may occur in association with administration of this drug. Sufficient attention should be paid when administrating.**

**[Precautions of Dosage and Administration]**

A high incidence of skin disorders has been reported in cases where this drug is administered at a dose exceeding the authorized dosage in the "Dosage and Administration" section. Attention should be paid to the use of concomitant drugs and authorized dosage should be complied with. If tablet(s) of this drug containing the exact dose adjusted based on the patient's body weight are not available, a combination of tablets that is as close as possible to the exact dose without exceeding it should be used.

See information on the precautions related lamotrigine, at the Pharmaceuticals and Medical Devices Information website
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html (In Japanese)

Product name (Name of Marketing Authorization Holder)
Lamictal Tablets 2 mg For Children, Lamictal Tablets 5 mg For Children, Lamictal Tablets 25 mg, 100 mg (GlaxoSmithKline K.K.)

## Table 3 "Dosage and Administration" of lamotrigine

Concomitant use of antiepileptics in epileptic patients (adult)

| | Concomitant use of VPA | No concomitant use of VPA | |
|---|---|---|---|
| | | (1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)] | (2) Concomitant use of other antiepileptic(s) [Note 2)] |
| Week1-2 | 25 mg on alternate days | 50 mg/day (once daily) | Same as the doses for the concomitant use of VPA |
| Week 3-4 | 25 mg/day (once daily) | 100 mg/day (twice daily in divided doses) | |
| Week 5 or later | Gradually increased by 25-50 mg every 1 or 2 weeks | Gradually increased by ≤ 100 mg every 1 or 2 weeks | |
| Maintenance dose | 100-200mg/day (twice daily in divided doses) | 200-400mg/day (twice daily in divided doses) | |

## Table 3 "Dosage and Administration" of lamotrigine (continued)

Concomitant use of antiepileptics in epileptic patients (children)

| | Concomitant use of VPA | | No concomitant use of VPA | |
|---|---|---|---|---|
| | Concomitant use of drug(s) that induces glucuronidation of lamotrigine Note 1) | No concomitant use of drug(s) that induces glucuronidation of lamotrigine Note 1) | (1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine Note 1) | (2) Concomitant use of other antiepileptic(s) Note 2) |
| Week1-2 | 0.15 mg/kg/day (once daily) | | 0.6 mg/kg/day (twice daily in divided doses) | Same as the doses for the concomitant use of VPA |
| Week 3-4 | 0.3 mg/kg/day (once daily) | | 1.2 mg/kg/day (twice daily in divided doses) | |
| Week 5 or later | Gradually increased by ≤ 0.3 mg/kg every 1 or 2 weeks | | Gradually increased by ≤ 1.2 mg/kg every 1 or 2 weeks | |
| Maintenance dose | 1-5mg/kg/day (up to 200 mg) (twice daily in divided doses) | 1-3mg/kg/day (up to 200 mg) (twice daily in divided doses) | 5-15 mg/kg/day (up to 400 mg) (twice daily in divided doses) | |

For suppression of recurrent/relapsed mood episode in patients with bipolar disorder (adult)

| | Lamotrigine alone | Concomitant use of VPA | No concomitant use of VPA Note 3) | |
|---|---|---|---|---|
| | | | (1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine Note 1) | (2) Concomitant use of other drug(s) Note 4) |
| Week1-2 | 25 mg/day (once daily) | 25 mg on alternate days | 50 mg/day (once daily) | Same as the doses for lamotrigine alone |
| Week 3-4 | 50 mg/day (once daily or twice daily in divided doses) | 25 mg/day (once daily) | 100 mg/day (twice daily in divided doses) | |

**Continued on the next page.**

## Table 3 "Dosage and Administration" of lamotrigine (continued)

For suppression of recurrent/relapsed mood episode in patients with bipolar disorder (adult) (continued)

| | Lamotrigine alone | Concomitant use of VPA | No concomitant use of VPA[Note 3)] | |
|---|---|---|---|---|
| | | | (1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine Note 1) | (2) Concomitant use of other drug(s) Note 4) |
| Week 5 | 100 mg/day (once daily or twice daily in divided doses) | 50 mg/day (once daily or twice daily in divided doses) | 200 mg/day (twice daily in divided doses) | Same as the doses for lamotrigine alone |
| Week 6 or later | 200 mg/day (up to 400 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤ 100 mg at an interval of 1 week or longer) | 100 mg/day (up to 200 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤ 50 mg at an interval of 1 week or longer) | At Week 6, 300 mg/day Week 7 or later, 300-400 mg/day (up to 400 mg/day) (twice daily in divided doses) (dose increase up to 100 mg at an interval of 1 week or longer) | |

Note 1) Drugs that induce glucuronidation of lamotrigine, including phenytoin, carbamazepine, phenobarbital, and priomidone

Note 2) Drugs that do not/may not affect the glucuronidation of lamotrigine, including zonisamide, gabapentine, and topiramate

Note 3) Patients receiving drug(s) that may not affect the glucuronidation of lamotrigine should follow the dosage and administration of lamotrigine used concomitantly with VPA .

Note 4) Drugs that do not affect the glucuronidation of lamotrigine, including lithium and olanzapine

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