



Investigation results

Lamotrigine

February 3, 2015

Product information

Brand Name (Marketing Authorization Holder)

Lamictal Tablets 2 mg for pediatrics, 5 mg for pediatrics, 25 mg, and 100 mg (GlaxoSmithKline K.K.)

Non-proprietary Name

lamotrigine

Indications

- Monotherapy for the following types of seizures in epileptic patients:
 - Partial seizures (including secondary generalized seizures)
 - Tonic-clonic seizures
- Concomitant therapy with antiepileptics for the following types of seizures in epileptic patients who have not sufficiently responded to other antiepileptics:
 - Partial seizures (including secondary generalized seizures)
 - Tonic-clonic seizures
 - Generalized seizures of Lennox-Gestaut syndrome
- Suppression of recurrent/relapsed mood episodes in patients with bipolar disorder

Estimated number of patients using lamotrigine

Approximately 376 000 (from the launch on December 12, 2008 to December 30, 2014)

Summary

Concerning serious skin disorders associated with lamotrigine, cautions have been included in the Warnings, Precautions for Dosage and Administration, Important Precautions, and Clinically Significant Adverse Reactions sections of the package insert since the initial marketing. The package insert, since the launch of lamotrigine, has included the caution that a high incidence of skin disorders



(rash etc.) was reported in cases where lamotrigine was administered at doses higher than recommended dosage and frequency of administration. For this reason, detailed instructions have been given about the dosage and administration during the initial phase of treatment as well as the dosage and administration and the interval of doses during dose titration before establishing the maintenance dose in relation to the drugs used concomitantly.

Cases of serious skin disorders reported after marketing of lamotrigine included many cases that failed to comply with the recommended dosage and frequency of administration. Therefore, the marketing authorization holder and the relevant medical associations have been periodically providing information to promote proper use of lamotrigine. In January 2012, the PMDA posted “Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine)-induced Serious Skin Disorders” on its website and has provided information on proper use of lamotrigine.

Under such circumstances, 7 fatal cases of serious skin disorders leading to death have been reported during the 4-month period from September to December 2014. In some of these cases, the information needed for evaluation of the causal relationship of serious skin disorders to lamotrigine was not sufficiently available or the status of the patient’s compliance with the recommended dosage and frequency of administration was unknown. For this reason, the PMDA instructed the marketing authorization holder to collect further information. The PMDA subsequently received additional information and reviewed the available evidence, and concluded that additional cautions against serious skin disorders associated with lamotrigine should be provided.

Evaluation results

Following an investigation based on opinions of expert advisors and available evidence, the PMDA concluded that this issue should be addressed in an urgent manner due to the following reasons:

- During the approximately 6-year and 1-month period from the launch on December 2008 to January 2015, a total of 16 fatal cases of serious skin disorders were reported, and there was a sharp increase of deaths (7 cases) during the latest approximately 4-month period.
- In 4 of the 7 fatal cases reported during the latest approximately 4-month period, a causal relationship of serious skin disorders to lamotrigine could not be ruled out. Furthermore, all of these 4 cases had failed to comply with the recommended dosage and frequency of administration. For example, the dose level during the initial phase of treatment was excessively high, administration of lamotrigine was started on consecutive days in concomitant use with



sodium valproate, or a dose increase was made too early. In the other 3 fatal cases, the information available is not sufficient enough to allow a judgment about the causal relationship of serious skin disorders to lamotrigine or to judge the status of compliance with the recommended dosage and frequency of administration before onset of skin disorders.

- The above-mentioned 4 fatal cases included cases for which early discontinuation of lamotrigine after appearance of the adverse reaction was not instructed before resulting in serious adverse reaction or the instruction of discontinuation was not followed.
- The serious skin disorders seen in the fatal cases were not confined to toxic epidermal necrolysis and oculomucocutaneous syndrome (Stevens-Johnson syndrome) listed in the Warnings section of the package insert. There were also cases where a causal relationship to drug-induced hypersensitivity syndrome (DIHS) could not be ruled out among these fatal cases. Therefore, caution about the possibility of DIHS development also needs to be widely urged.

It is a serious issue that the fatal cases were reported in cases where the drug were used in noncompliance with the recommended dosage and frequency of administration of lamotrigine, despite the fact that cautions on serious skin disorders associated with lamotrigine had been included the Warnings section in the package insert and that the information for proper use of lamotrigine had been repeatedly provided after marketing of lamotrigine. It is now necessary to fully inform of the information that serious skin disorders associated with lamotrigine may occur, resulting in fatal outcomes in some cases. In addition, a further alert is also necessary to fully inform healthcare professionals of the following: (1) the importance of complying with the recommended dosage and frequency of administration including instructions on the initial dose level and the dose and interval of dose increase to reduce the risk for serious skin disorders, and (2) the necessity of making efforts towards early detection and treatment of serious skin disorders through immediate discontinuation of lamotrigine upon appearance of rash or other early signs of serious skin disorders, and cooperating with dermatology specialists for appropriate diagnosis and treatment.