

Dear Healthcare Professionals Letter of Rapid Safety Communication BLUE LETTER

Serious skin disorders suggestively caused by Lamictal tablets for pediatrics 2 mg and 5 mg, and Lamictal tablets 25 mg and 100 mg

In approximately 4 months from September 2014 to December 2014, a total of 4 cases of serious skin disorders leading to death, in which causality between the serious skin disorders and the drug could not be ruled out, have been reported in patients treated with Lamictal (lamotrigine) in Japan. In all 4 cases, treatment with Lamictal did not comply with the recommended dosage and frequency of administration as stated in the package insert. In addition, discontinuance of Lamictal after skin disorder were not taken until the symptoms became serious. Considering this situation, the Warnings subsection in the Precautions section of the package insert will be updated to further ensure the proper use of Lamictal.

Since the launch of Lamictal on December 12, 2008 till January 26, 2015, a total of 16 cases of serious skin disorders leading to death, including the above cases, have been reported in patients treated with Lamictal in Japan (the estimated number of users is approximately 376 000 patients*).

(*NOTES: the estimated number of users is calculated for the period from December 2008 to December 31, 2014)

Please pay attention to the following points for the use of Lamictal.

Healthcare professionals should comply with the dosage and administration as stated in the package insert of this drug.

The incidence of skin disorders was increased when this drug was administered at doses higher than recommended dosage and frequency of administration.

- During the initial phase of treatment, this drug should not be used at doses higher than the recommended dosage and frequency of administration.
- When used concomitantly with sodium valproate, this drug should be administered on alternate days for the first 2 weeks (only for adult patients).
- This drug should not be used at doses higher than recommended dosage and frequency of administration during dose titration before establishing the maintenance dose.
- A dose increase should not be attempted earlier than the specified timing.

Healthcare professionals should make an effort towards early detection and treatment of skin disorders.

- The following symptoms in addition to a rash might indicate the development of a serious skin disorder. Administration of this drug should be discontinued immediately.
 - Pyrexia (higher than 38 °C)
 - Lip/oral mucosa erosion
 - General malaise
 - Ocular hyperaemia
 - Pharyngodynia
 - Lymphadenopathy, etc.
- Delay in the treatment of skin disorders might lead to a serious outcome. Healthcare professionals should consult with a dermatologist at an early stage, and appropriate measures should be taken.
- Patients and their family should be advised to see a doctor immediately and tell a doctor or pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

Revisions of Precautions in the Package Insert

Revised	Current
<p>Warnings Serious skin disorders <u>with general symptoms</u> such as <u>toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens–Johnson syndrome), and drug-induced hypersensitivity syndrome</u> may occur in patients treated with this drug, <u>and result in fatal outcomes in some cases.</u> Attention should be paid to <u>the following items:</u> (See Precautions for dosage and administration, Important precautions, Adverse reactions, and Clinical studies sections)</p> <ol style="list-style-type: none"> 1. <u>Dosage and frequency of administration in the package insert of this drug should be followed because the incidence of skin disorders is increased when this drug is administered at doses higher than recommended dosage and frequency of administration.</u> <ol style="list-style-type: none"> (1) <u>During the initial phase of treatment, this drug should not be used at doses higher than recommended dosage and frequency of administration. When used concomitantly with sodium valproate, this drug should be administered on alternate days for the first 2 weeks (only for adult patients).</u> (2) <u>This drug should not be used at doses higher than recommended dosage and frequency of administration during dose titration before establishing the maintenance dose. A dose increase should not be attempted earlier than the specified timing.</u> 2. <u>If a rash occurs, healthcare professionals should consult with a dermatologist in an early stage, and appropriate measures should be taken. The following symptoms in addition to a rash might indicate a serious skin disorder; therefore, administration of this drug should be discontinued immediately:</u> <u>Pyrexia (higher than 38 °C), ocular hyperaemia, lip/oral mucosa erosion, pharyngodynia, general malaise, lymphadenopathy, etc.</u> 3. <u>Careful attention should be paid to pediatric patients because an increased incidence of serious skin disorders has been reported in pediatric patients.</u> 4. <u>Patients or their families should be advised to see their doctor immediately when a rash and/or the above symptoms occur.</u> 	<p>Warnings Serious skin disorders such as toxic epidermal necrolysis and oculomucocutaneous syndrome (Stevens–Johnson syndrome) may occur in patients treated with this drug. Careful attention should be paid in administration of this drug. (See Precautions for dosage and administration, Important precautions, Adverse reactions, and Clinical studies sections)</p>
<p>Precautions 2. Important precautions</p> <ol style="list-style-type: none"> (1) A rash in patients treated with this drug is commonly <u>maculo-papular*</u>. The incidence of serious skin disorders is increased for the first 8 weeks of the treatment. The high incidence has been reported also in patients concomitantly treated with sodium valproate or in pediatric patients. Careful attention should be paid in administration of this drug. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. (See Warnings, Precautions for dosage and administration, Adverse reactions, and Clinical studies sections) 	<p>Precautions 2. Important precautions</p> <ol style="list-style-type: none"> (1) A rash in patients treated with this drug is commonly maculo-papular. The incidence of serious skin disorders is increased for the first 8 weeks of the treatment. The high incidence has been reported also in patients concomitantly treated with sodium valproate or in pediatric patients. Careful attention should be paid in administration of this drug. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. (See Warnings, Precautions for dosage and administration, Adverse reactions, and Clinical studies sections)

5. Adverse reactions

(1) Clinically significant adverse reactions

2. As symptoms of **drug-induced hypersensitivity syndrome** (frequency unknown), a rash and/or pyrexia may occur at an early stage followed by various general symptoms including lymphadenopathy, face oedema, blood disorders (eosinophilia, leukocytosis, atypical lymphocytes), and organ disorders (hepatic dysfunction etc.). Signs and symptoms of drug-induced hypersensitivity syndrome are of late-onset. If signs of drug-induced hypersensitivity syndrome are observed, administration should be discontinued immediately and appropriate measures taken.

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_____ : revision by PFSB/SD Notification

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*: The Japanese translation has been changed a little

Inquiry

Customer Care Center of GlaxoSmithKline K.K.

- Toll-free phone number: 0120-563-607
From February 4 through February 13, 2015:
9:00 – 18:00 (weekday) and 9:00 – 17:00 (weekend and national holiday)
After February 14, 2015:
9:00 - 18:00 (closed on Saturday, Sunday, national holiday, and non-business day)
- Toll-free FAX number: 0120-561-047 (24 hours)