

## Lamotrigine and photosensitivity

### Introduction

Lamotrigine (Lamictal®) is indicated *for the treatment of partial epilepsy and generalized epilepsy and for the treatment of syndrome of Lennox-Gastaut in adults and children older than 12 years*. In addition, in children of 2-12 years, the drug is indicated as *adjunctive therapy for the treatment of partial epilepsy and generalized epilepsy, as adjunctive therapy for the treatment of syndrome of Lennox-Gastaut and as monotherapy for the treatment of absence epilepsy*.

Furthermore lamotrigine is indicated in *adults for the prophylaxis of depressive episodes in patients with bipolar disorder* [1]. Lamotrigine was granted market authorisation in the Netherlands in 1996 (Lamictal®) [1].

Photosensitivity induced by exogenous agents is a process in which chemicals or drugs that are ingested or applied to the skin promote a photosensitivity reaction when the individual is exposed to sunlight. It can be divided into phototoxic and photoallergic reactions. Phototoxic and photoallergic reactions differ in their clinical features and causative agents. Phototoxicity results from direct tissue or cellular damage following ultraviolet irradiation of a phototoxic agent that has been ingested or applied to the skin. Phototoxicity can occur in any individual in whom the threshold concentration of the chemical or drug has been reached. By contrast, photoallergy is a cell-mediated immune response elicited by small amounts of compound in previously sensitized individuals [2].

The majority of drug-induced photosensitivity reactions are phototoxic. Phototoxic reactions appear as an exaggerated sunburn. The reaction usually evolves within minutes to hours of sun exposure and is restricted to exposed skin.

Photoallergic reactions are typically pruritic, eczematous eruptions in sun-exposed areas of skin that develop 24 to 48 hours after sun exposure and do not necessarily have to be restricted to the sunlight exposed skin only [2].

### Reports

From January 1999 until November 2019 the Netherlands Pharmacovigilance Centre Lareb received three reports of photosensitivity associated with the use of lamotrigine.

Table 1. Reports of photosensitivity associated with lamotrigine in the Lareb database

No., ID, sex, age, primary source	Drug, Dosage, Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1, NL-LRB-23489, Dermatologist, female, 60-70 Years	Lamotrigine 100Mg dd Epilepsy, unspecified		Photosensitivity reaction (itching exanthema on arms and legs after sunlight exposure)	3 Months	Dose Not Changed	Not recovered
2, NL-LRB-24001, General Practitioner and Pharmacist, female, 20-30 Years	Lamotrigine 50Mg 2dd Epilepsy, unspecified	Clobazam, Carbamazepine, Valproic acid	Photosensitivity reaction	Unknown, reaction occurred while dose was being increased	Unknown	Unknown
3, NL-LRB-00286661, Neurologist, male, 20-30 Years	Lamotrigine 25Mg 2dd Epilepsy		Photosensitive rash (rash, mostly on bodyparts that had been exposed to sunlight)	3 Weeks	Drug Withdrawn	Recovering

Additional information on the cases:

1. The reporter comments that since lamotrigine is the only drug that the patient can tolerate, they advised her to continue with this for the time being, supplemented in the summer months with sun protection through clothing and Sun Protection Factor (SPF) (Contralum Ultra®).

Furthermore, they comment that with the current data, it is not possible to differentiate these reactions from a so-called "polymorphic light-eruption".

3. The reaction occurred 3 weeks after start and a few days after the dose was increased to 75 mg. The rash occurred mainly on parts of the skin that were exposed to sunlight, and a minor rash occurred on other parts of the body. The drug was withdrawn and the patient is recovering (5 days after withdrawal).

## Other sources of information

### SmPC

Skin reactions, including severe potential life-threatening ones are described in the Dutch SmPC of lamotrigine. The SmPC of lamotrigine does not mention photosensitivity as an adverse reaction [1]. The US SmPCs of lamotrigine shows a table with treatment-emergent adverse event incidence in placebo-controlled adjunctive trials in paediatric patients with epilepsy (Events in at least 2% of patients treated with lamotrigine) and numerically more frequent than in the placebo group); there were 2 cases of photosensitivity in the lamotrigine group and none in the placebo group [3].

### Literature

Two cases are described by Bozikas et al [4]. A 42-year-old man with a diagnosis of schizoaffective disorder (bipolar type), received lamotrigine, 25 mg t.i.d., coadministered with haloperidol, 20 mg b.i.d. His dose of lamotrigine was titrated gradually within a month. One year later, his dose of lamotrigine was raised to 100 mg b.i.d., whereas his dose of haloperidol stayed the same. Three months later, an acute maculopapular rash with itching appeared, which subsided after his lamotrigine treatment was interrupted. The day before the rash appeared, he had been exposed to sunlight while doing agricultural work. A 30-year-old woman with a diagnosis of bipolar disorder type I (her most recent episode was manic), received lamotrigine as a prophylactic therapy. Her lamotrigine dose was titrated gradually within 1 month up to 100 mg b.i.d.. Six months later, she developed an acute maculopapular rash with itching. The day before the rash appeared, she had been exposed to the light of a solarium. The rash subsided after her treatment with lamotrigine was discontinued.

The authors conclude that the absence of a history of skin disease and the subsidence of the rash after the discontinuation of lamotrigine lead to the conclusion that the rash was a side effect of the drug and that patients who receive lamotrigine should avoid prolonged exposure to sunlight.

### Databases

Table 2. Reports of photosensitivity associated with the use of lamotrigine in the Lareb, WHO and Eudravigilance database [5;6]

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	Lamotrigine	Photosensitivity	3	2.0 [0.6 - 6.3]
WHO	Lamotrigine	Photosensitivity	175	1.7 [1.5 - 1.9]
Eudravigilance	Lamotrigine	Photosensitivity	62	1.8 [1.4 - 2.4]

For the WHO cases, 132 contained a single suspect drug. There were 28 cases with a dechallenge.

Table 3. Prescription data (number of users) [7].

Drug	2014	2015	2016	2017	2018
Lamotrigine	19,669	20,766	21,801	22,484	23,333

### Mechanism

Lamotrigine belongs to a class of chlorinated aromatic compounds that are generally more likely to trigger phototoxicity than similar nonchlorinated drugs. In an experimental setting, lamotrigine absorbs UV light, generating singlet oxygen ( $^1O_2$ ). A small production of superoxide radical anion was also detected in acetonitrile. The authors conclude that lamotrigine is a moderate photosensitizer producing phototoxicity and oxidizing linoleic acid [8].

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of photosensitivity associated with the use of lamotrigine. In two cases a direct relation between sunlight exposure and the occurrence of the photosensitivity reaction is described. This was also described in two literature cases [4]. There is a possible mechanism and disproportionality of the association in the WHO and EMA databases. However, the diagnosis of photodermatos has only been confirmed by a dermatologist in one of the cases. Photodermatos also has a relatively high background incidence, making it more difficult to

assess the causality between lamotrigine and photosensitivity. The duration and frequency of sun exposure (before and after lamotrigine use) are not clearly described in the cases. The number of cases in the Lareb database is low. However, some well-documented cases were also identified in the Eudravigilance database.

Since photosensitivity reactions can be avoided if patients are aware of the possible risk, attention is warranted for the association between lamotrigine and photosensitivity.

#### Reference List

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5. Eudravigilance database. <http://bi.eudra.org> (access restricted) 2019.
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7. GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. <http://www.gipdatabase.nl> (last updated 2019 7-10-2019, cited 5-12-2019).
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*This signal has been raised on February 6, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbq-meb.nl](http://www.cbq-meb.nl)*