

## Lamictal®

M R F

GlaxoSmithKline

Tuggtablett/dispergerbar tablett 2 mg

(Vit till gulvit och kan vara lätt marmorerad. Den luktar svartvinbär. Tabletten är 4,8 mm lång, rund och märkt "LTG" ovanför siffran "2" på ena sidan och med två överlappande ovaler i rät vinkel på den andra sidan.)

Antiepileptikum

### Aktiv substans:

Lamotrigin

### ATC-kod:

N03AX09

Läkemedel från GlaxoSmithKline omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Lamotrigin

Miljörisk: Användning av lamotrigin har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Lamotrigin är potentiellt persistent.

Bioackumulering: Lamotrigin har låg potential att bioackumuleras.

### Detaljerad miljöinformation

#### Detailed background information

#### Environmental Risk Classification

#### *Predicted Environmental Concentration (PEC)*

PEC is calculated according to the following formula:

$$PEC (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.5 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

$$PEC = 0.47 \mu\text{g/L}$$

Where:

A = 3,150.23 kg (total sold amount API in Sweden year 2015, data from IMS Health). Reduction of A may be justified based on metabolism data.

R = 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)

P = number of inhabitants in Sweden =  $9 \cdot 10^6$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. I)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. I)

### ***Predicted No Effect Concentration (PNEC)***

#### **Ecotoxicological studies**

*Green Algae (Scenedesmus subspicatus):*

IC50 96h (growth) = 39,700 µg/L (OECD 201) (Reference 7)

NOEC = 7,500 µg/L

*Water flea (Daphnia magna):*

Acute toxicity

EC50 48 h (immobility) = 56,000 µg/L (OECD 202) (Reference 8)

*Water flea (Ceriodaphnia dubia):*

Chronic toxicity

NOEC 8 days (reproduction) = 10,000 µg/L (USEPA 1002) (Reference 10)

*Rainbow Trout (Oncorhynchus mykiss):*

Acute toxicity

LC50 96 h (lethality) = 85,000 µg/L (OECD 203) (Reference 9)

*Fish:*

Chronic toxicity

No data

*Other ecotoxicity data:*

*Microorganisms in activated sludge:*

EC50 3 h (inhibition) = 1,000,000 µg/L @ 3 hrs (OECD 209) (Reference 5)

$PNEC = 7,500/50 = 150 \mu\text{g/L}$

*PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for alga (= 7 500 µg/L) has been used for this calculation since it is the most sensitive of the three tested species*

#### **Environmental risk classification (PEC/PNEC ratio)**

$PEC/PNEC = 0.47/150 = 0.0031$ , i.e.  $PEC/PNEC \leq 0.1$  which justifies the phrase "Use of lamotrigine has been considered to result in insignificant environmental risk."

#### **Degradation**

##### **Biotic degradation**

*Ready degradability:*

<1% degradation in 28 days (TAD 3.11). (Reference 4)

*Inherent degradability:*

<10% degradation in 28 days (OECD 302). (Reference 6)

**Abiotic degradation**

*Hydrolysis:*

No data

*Photolysis:*

No data

*Justification of chosen degradation phrase:*

Lamotrigine is not readily degradable or inherently degradable. The phrase "Lamotrigine is potentially persistent" is thus chosen.

**Bioaccumulation**

*Partitioning coefficient:*

Log Dow = 1.54 at pH 7.4 (TAD 3.02). (Reference 3)

Log Dow at pH 5 < 1

Log Dow at pH 7 = 1.4

Log Dow at pH 9 = 1.4

*Justification of chosen bioaccumulation phrase:*

Since log Dow < 4 at pH 7, the substance has low potential for bioaccumulation.

**Excretion (metabolism)**

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

The apparent plasma clearance in healthy subjects is approximately 30 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of lamotrigine-related material is excreted in faeces (Reference 2).

**PBT/vPvB assessment**

Lamotrigine does not fulfil the criteria for PBT and/or vBvP.

All three properties, i.e. 'P', 'B' and 'T' are required in order to classify a compound as PBT (Reference 1). Lamotrigine does not fulfil the criteria for PBT and/or vBvP based on log Pow < 4.

**Please, also see Safety data sheets on**<http://www.msds-gsk.com/ExtMSDSlist.asp>.

**References**

1. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
2. Pharmacokinetic properties: Metabolism and Elimination. Summary of Product Characteristics Lamictal (Lamotrigine). GlaxoSmithKline, April 2013.
3. Lamictal Environmental Information Document. Report No. GCPV/91/0005-01. Burroughs Wellcome Co., January 1993.
4. Blasberg J. Aerobic Biodegradation in Water Using 14-C-Lamotrigine. Report No. 40510. ABC Laboratories, November 1992.
5. Lamotrigine: Activated Sludge, Respiration Inhibition Test. Test No. 91-04-232-01. AATCC Testing Services, April 1991.
6. Stewart KM, Smyth DV, Kent SJ. Lamotrigine: Determination of Inherent Biodegradability (Zahn-Wellens test). Report No. BL7683/B. Brixham Environmental Laboratory, October 2004.
7. Kent SJ and Swarbrick RH. Lamotrigine: Toxicity to the green alga *Selenastrum capricornutum*. Report No. BL7681/B. Brixham Environmental Laboratory, August 2004.
8. Kent SJ and Swarbrick RH. Lamotrigine: Acute Toxicity to *Daphnia magna*. Report No. BL7680/B. Brixham Environmental Laboratory, July 2004.
9. Kent SJ and Swarbrick RH. Lamotrigine: Acute Toxicity to rainbow trout (*Oncorhynchus mykiss*). Report No. BL7682/B. Brixham Environmental Laboratory, August 2004.
10. Young BE and Kent SJ. Lamotrigine: Determination of the 3 brood (7 day) chronic toxicity to *Ceriodaphnia dubia*. Report No. BL8147/B. Brixham Environmental Laboratory, March 2006.