

## ALIMTA

M R EF

**Lilly**

Pulver till koncentrat till infusionsvätska, lösning 100 mg  
(Tillhandahålls ej) (vitt till ljus gult eller gröngult, frystorkat  
pulver)

Cytostatikum

**Aktiv substans:**

Pemetrexed

**ATC-kod:**

L01BA04

Läkemedel från Lilly omfattas av Läkemedelsförsäkringen.  
Läkemedlet distribueras också av företag som inte omfattas av  
Läkemedelsförsäkringen, se Förpackningar.

## Miljöpåverkan

### Pemetrexed

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

Nedbrytning: Pemetrexed bryts ned i miljön.

Bioackumulering: Pemetrexed har låg potential att bioackumuleras.

# Detaljerad miljöinformation

## Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

$$\begin{aligned}\text{PEC } (\mu\text{g/L}) &= (A \times 1000000000 \times (100 - R)) \div (365 \times P \times V \times D \times 100) \\ &= 0,0000015 \times A \times (100 - 0) \\ &= 0,0000015 \times 4,4678 \times 100 \\ &= 0,0003 \mu\text{g/L}\end{aligned}$$

Where:

A = 2,070550079 kg (total amount sold in Sweden in 2020 as pemetrexed, data from IQVIA). This number is not adjusted for metabolism.

| API form                         | Sales in 2020 kg |
|----------------------------------|------------------|
| pemetrexed disodium heptahydrate | 2,89443          |
| Pemetrexed                       | 2,070550079*     |

\*calculated by multiplying the kg of pemetrexed disodium heptahydrate sold by the molecular weight ratio of pemetrexed free acid:pemetrexed disodium heptahydrate salt (427,411:597,48)

R = Assumed 0% removal rate in a sewage treatment plant

P = 9000000 population of Sweden

V = 200 L of wastewater per capita per day (ECHA, 2016)

D = 10 dilution of wastewater by surface water flow (ECHA, 2016)

### Predicted No Effect Concentration (PNEC)

#### Ecotoxicological Studies

Algae (*Pseudokirchneriella subcapitata*) (OECD 201) (Study 1982.6301)

EC50 72 h (yield) = 17000 µg/L

NOEC 72 h (yield) = 4000 µg/L

Crustacean (*Daphnia magna*)

Acute toxicity (FDA 4.08)

EC50 48 h (immobilization) = 462000 µg/L (Study C00497)

Chronic toxicity (OECD 211)

NOEC 21 days (survival, reproduction, growth) = 1200 µg/L (Study 1982.6303)

Rainbow trout (*Oncorhynchus mykiss*)

Acute toxicity (FDA 4.11)

LC50 96 h (mortality) > 1099600 µg/L (Study F00297)

Fathead minnow (*Pimephales promelas*)

Chronic toxicity (OECD 210)

NOEC 5 d embryos + 28 d larvae (mortality, growth) = 13000 µg/L (Study 1982.6302)

### **Calculation of PNEC**

$PNEC = 1200 \mu\text{g/L} \div 10$

$PNEC = 120 \mu\text{g/L}$

The PNEC was calculated from the NOEC for daphnia because daphnia are the most sensitive of the species tested in long-term studies. An assessment factor of 10 was used because long-term results were available for species from three trophic levels: fish, daphnids and algae.

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

$PEC/PNEC = 0,0003 \div 120 = 0,000003$

The PEC/PNEC ratio of less than 0,1 justifies the phrase “Use of pemetrexed has been considered to result in insignificant environmental risk.”

## Degradation

### Biotic Degradation

#### *Ready Degradability:*

In a ready biodegradability test, 20% of the theoretical carbon evolved over 29 days as carbon dioxide (OECD 301). (Study 1982.6300)

#### *Inherent degradability:*

Pemetrexed was readily and extensively transformed when incubated with activated sewage sludge (OECD 302A). More than 90% of  $^{14}\text{C}$ -labeled pemetrexed disappeared after 1 hour and no pemetrexed was present by 24 hours. There were several transformation products that appeared and then disappeared during a 28-day study as measured by HPLC/RAM. By the end of the 28-day study, 18.4% of the applied radioactivity had evolved as  $^{14}\text{CO}_2$ . (Study 1982.6337)

#### *Simulation studies:*

Pemetrexed was also transformed in two static, aerobic water-sediment systems (OECD 308). On Day 0,  $^{14}\text{C}$ -pemetrexed was dosed into test chambers containing sediment and overlying water. On Days 0, 3, 14, 28, 55 and 100, chambers were sacrificed and the sediment and water separated. The sediments were extracted with 80:20:0.5 acetonitrile:water:hydrochloric acid. The sediment extracts and the overlying water were evaluated by HPLC-RAM. Effluent gasses from the test chambers were monitored for volatile radioactivity.

On Day 0, approximately 99% of the dosed radioactivity was in the water and approximately 90% of the dosed radioactivity was  $^{14}\text{C}$ -pemetrexed. On Day 3, 69% to 76% of the radioactivity was in water, 19% to 20% was in the sediment extracts, less than 1% had

evolved as  $^{14}\text{C-CO}_2$ , and 6% to 12% could not be extracted from sediment. Characterization of 89% and 94% of the dosed radioactivity on Day 3 (the sum of radioactivity in the water and sediment extracts) by HPLC-RAM demonstrated that pemetrexed had disappeared from the water-sediment system and that the radioactivity consisted of several transformation products. The DT50 of pemetrexed from the water-sediment systems was less than 3 days and most of the disappearance was due to degradation. Over the rest of the 100-day study, further degradation of the transformation products was observed and 8% and 14% of the applied radioactivity in the two sediment systems was recovered as evolved  $^{14}\text{CO}_2$ . By the end of the study, 40% and 27% of the applied radioactivity was nonextractable from the sediment. (Study 1982.6307)

## **Abiotic Degradation**

### *Hydrolysis:*

Less than 10% disappearance of pemetrexed was observed when incubated in the dark in water buffered at pH 4, 7 or 9 for 5 days at 50°C (OECD 105). (Study 1982.6305)

### **Justification of the degradation phrase:**

Pemetrexed is inherently biodegradable in activated sewage sludge and its half-life in water-sediment systems was less than 3 days. Therefore, pemetrexed is classified as being degraded in the environment.

## **Bioaccumulation**

### *Partitioning coefficient:*

$\log K_{ow} < 0.3$  (OECD 117) (Study 1982.6304)

The result of this HPLC estimation method for the partitioning coefficient is supported by the aqueous solubility of pemetrexed in water buffered at pH 7 and 9: 101.5 and 89.4 g/L, respectively (OECD 105). (Study EC9707)

#### **Justification of chosen bioaccumulation phrase:**

Because the log Kow is less than 4, pemetrexed has a low potential for bioaccumulation.

#### **Excretion (metabolism)**

Pemetrexed is not metabolized to an appreciable extent, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. (Alimta Package Insert; <http://pi.lilly.com/us/alimta-pi.pdf>).

#### **PBT/vPvB ASSESSMENT**

Because it does not have a high potential to bioaccumulate and is not persistent, pemetrexed does not fulfill the criteria for PBT and, therefore, is not regarded as a PBT/vPvB substance.

#### **References**

Alimta Package Insert. 2013. <http://pi.lilly.com/us/alimta-pi.pdf>.

Alimta®. Safety Data Sheet. Issue date: 11-20-2014.

<http://ehs.lilly.com/msds/Alimta.pdf>.

ECHA, European Chemicals Agency. 2016 Guidance on information requirements and chemical safety assessment. Chapter R.16: Environmental Exposure Estimation. Version 3.0

[https://echa.europa.eu/documents/10162/13632/information\\_requirements](https://echa.europa.eu/documents/10162/13632/information_requirements)  
Study 1982.6300. 2008. Pemetrexed (LY231514) - Determination of Biodegradability Based on OECD Method 301B (CO<sub>2</sub> Evolution Test). Eli Lilly and Company.

Study 1982.6301. 2008. Pemetrexed (LY231514) – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline 201. Eli Lilly and Company.

Study 1982.6302. 2013. Pemetrexed (LY231514) – Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*), Following OECD Guideline #210. Eli Lilly and Company.

Study 1982.6303. 2009. Pemetrexed (LY231514) – Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Static-Renewal Conditions, Following OECD Guideline #211. Eli Lilly and Company.

Study 1982.6304. 2008. Pemetrexed (LY231514) - Determination of the Adsorption Coefficient,  $K_{oc}$ , following OECD Guideline 121 and Determination of n-Octanol/Water Partition Coefficient,  $P_{ow}$ , Following OECD Guideline 117. Eli Lilly and Company.

Study 1982.6305. 2008. Determination of the Abiotic Degradation of Pemetrexed (LY231514) by Hydrolysis at Three Different pH Values Following OECD Guideline 111. Eli Lilly and Company.

Study 1982.6307. 2009. [ $^{14}\text{C}$ ]Pemetrexed ([ $^{14}\text{C}$ ]LY231514) - Aerobic Transformation in Aquatic Sediments Systems Following OECD Guideline 308. Eli Lilly and Company.

Study 1982.6337. 2009. [ $^{14}\text{C}$ ]Pemetrexed ([ $^{14}\text{C}$ ]LY231514) - Determination of the Inherent Biodegradability and Adsorption by the SCAS Test, Modified from OECD Guideline 302A. Eli Lilly and Company.

Study C00497. 1997. Pilot *Daphnia magna* Study Conducted with LY231514 Disodium. Eli Lilly and Company.

Study EC9707. 1997. A Study to Determine the Solubility of LY231514 Disodium. Eli Lilly and Company.

Study F00297. 1997. Pilot Rainbow Trout Study Conducted with LY231514 Disodium. Eli Lilly and Company.