

**GILENYA<sup>®</sup>****M R F<sub>f</sub>****Novartis**

Kapsel, hård 0,5 mg

(16 mm kapsel med klargul, ogenomskinlig överdel och vit, ogenomskinlig underdel; märkt med "FTY0.5 mg" tryckt med svart färg på överdelen och med två ränder tryckta radiellt med gul färg på underdelen.)

Selektiva immunsuppressiva medel

**Aktiv substans:**

Fingolimod

**ATC-kod:**

L04AE01

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

## Miljöpåverkan

### Fingolimod

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

Nedbrytning: Fingolimod bryts ned i miljön.

Bioackumulering: Fingolimod 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:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

$$\text{PEC} = 0.0000189 \mu\text{g/L} = 0.0189 \text{ ng/L}$$

Where:

A = 0.1378 kg fingolimod hydrochloride (total sold amount API in Sweden year 2021, data from IQVIA).

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0, if no data is available.

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

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

#### Predicted No Effect Concentration (PNEC)

#### Ecotoxicological studies

*Algae (Selenastrum capricornutum) (OECD 201) (NOTOX Project 305101):*

EC<sub>10</sub> 72 h (growth rate) = 41.9 µg/L

NOEC 72 h (growth rate) = 20.3 µg/L

*Crustacean (Waterflea, Daphnia magna):*

Acute toxicity

EC50 48 h (immobilisation) = 120.0 µg/L (OECD202) (NOTOX Project 305112)

Chronic toxicity

NOEC 21 days (mortality of parent daphnids) = 89.0 µg/L (OECD 211) (RCC Study B54000)

*Fish (Zebrafish, Danio rerio):*

Chronic toxicity

NOEC 34 days (survival of larvae and juvenile fish) = 90.0 µg/L (OECD 210) (RCC Study B54022)

*Other ecotoxicity data:*

*Bacterial respiration inhibition (activated sludge microorganisms)*

EC<sub>10</sub> 3 h = 20.0 mg/L (OECD209), (NOTOX Project 305123)

PNEC = 20.3 µg/L / 10 = 2.03 µg/L = 2030 ng/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used, if chronic toxicity values for 3 trophic levels are available. NOEC from green algae growth inhibition (OECD 201) 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 = 0.0189 ng/L / 2030.0 ng/L =  $9.2 \times 10^{-6}$ , i.e. PEC/PNEC  $\leq 0.1$  which justifies the phrase "Use of fingolimod has been considered to result in insignificant environmental risk."

## **Degradation**

### **Biotic degradation**

#### *Ready degradability:*

0 % degradation in 28 days, not readily biodegradable (OECD301 B). (NOTOX Project 305134)

#### *Transformation in water-sediment systems:*

DT50 in total system = 0.35 – 0.39 days (OECD 308). (Harlan Laboratories Study B53998)

Study duration: 28 days

The DT50 given above refers to the loss of initially applied parent substance (initially applied radioactivity) due to its transformation, mineralization and/or irreversible binding to sediments. At the end of the study (day 28) only 0.7-0.8 % of applied radioactivity remained in the total system as parent API. Sediments were submitted to up to three extraction steps using acetonitrile/water (4:1; v/v) at room temperature. From day 1 onwards, Soxhlet extraction using acetonitrile/water (4:1; v/v) for 4 hours was additionally performed on the extracted sediments.

#### *Justification of chosen degradation phrase:*

According to the classification scheme proposed for the OECD308 studies in the update of the 'Environmental classification of pharmaceuticals at [www.fass.se](http://www.fass.se) - Guidance for pharmaceutical companies' of 2012, fingolimod can be classified as 'Fingolimod is degraded in the environment'.

## **Bioaccumulation**

*Partitioning coefficient:*

Log D = 3.4 (pH 7.4; dual-phase potentiometric titration)  
(RD-2010-00593)

*Justification of chosen bioaccumulation phrase:*

Since logD at pH 7.4 < 4, fingolimod has low potential for bioaccumulation.

## **Excretion (metabolism)**

After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the feces with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%. (Novartis Core Data Sheet, GILENYA® (fingolimod))

## **References**

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. [http://guidance.echa.europa.eu/docs/guidance\\_document/informa](http://guidance.echa.europa.eu/docs/guidance_document/informa)
- NOTOX Project 305101: Fresh water algal growth inhibition test with FTY720/DS. Final report: 28 February 2001.
- NOTOX Project 305112: Acute toxicity study in *Daphnia magna* with FTY720/DS (static). Final report: 28 February 2001.

- RCC Study B54000: FTY720 DS: Effect on survival and reproduction of *Daphnia magna* in a semi-static test over three weeks. Final report: 09 July 2008.
- RCC Study B54022: FTY720 DS: Toxic effects to zebra fish (*Brachydanio rerio*) in an early-life stage toxicity test. Final report: 08 September 2008.
- NOTOX Project 305123: Activated sludge respiration inhibition test with FTY720/DS (contact time: 3 hours). Final report: 20 November 2000.
- NOTOX Project 305134: Determination of 'ready' biodegradability: carbon dioxide (CO<sub>2</sub>) evolution test (modified Sturm test) with FTY720/DS. Final report: 18 December 2000.
- RD-2010-00593: Faller B, Rodde S, Domange N. FTY720: Lipophilicity profile. Novartis Pharma AG Basel, Switzerland. Research Study report no RD-2010-00593; 02 July 2010.
- Harlan Laboratories Study B53976: 14C-FTY720 DS: Adsorption/desorption. Final report: 23 January 2009.
- Harlan Laboratories Study B53998: 14C-FTY720 DS: Route and rate of degradation in aerobic aquatic sediment systems. Final report: 20 January 2009.
- Novartis Core Data Sheet for GILENYA<sup>®</sup> (fingolimod), Version 3.4, 21 January 2019