

Ergenyl

Sanofi AB

Enterotablett 100 mg

Avregistreringsdatum: 2022-01-31 (Tillhandahålls ej) (vit, rund, kupad 7 mm)



Antiepileptikum

Aktiv substans:

Valproinsyra

ATC-kod:

N03AG01

För information om det avregistrerade läkemedlet omfattas av Läkemedelsförsäkringen, kontakta Läkemedelsförsäkringen.

Läs mer om avregistrerade läkemedel

Miljöpåverkan

Valproinsyra

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

Nedbrytning: Valproinsyra är potentiellt persistent.

Bioackumulering: Valproinsyra har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.245 \mu\text{g/L}$$

Where:

A = 1636.091 kg (total sold amount API in Sweden year 2019, data from IQVIA)

R = 0% removal rate (due to 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 of dilution of waste water by surface water flow = 10 (ECHA default) (Ref I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Pseudokirchneriella subcapitata):

EC₅₀ 72 h (biomass) = >100 000 µg/L

EC₅₀ 72 h (growth rate) = >100 000 µg/L

NOEC = 100 000 µg/L

(OECD 201)

(Ref II)

Crustacean (Daphnia magna):

EC₅₀ 48 h (immobilization) = >100 000 µg/L

NOEC 48 h (immobilization) = >100 000 µg/L

(OECD 202)

(Ref III)

Chronic toxicity crustacean (Daphnia magna)

NOEC, EC₅₀, EC₁₀ 21 d (reproduction) ≥ 8870 µg/L

(OECD 211)

(Ref IV)

Fish (Danio rerio):

LC₅₀ 96 h (lethality) = 66 000 µg/L

(OECD 236)

(Ref V)

Chronic toxicity fish (Danio rerio)

NOEC 30 d (mortality) ≥ 10 200 µg/L

(OECD 210)

(Ref VI)

Other ecotoxicity data:

PNEC = 887 µg/L

The PNEC is calculated with the following formula: lowest EC₁₀ or NOEC/10 (Assessment factor justification: three long-term toxicity endpoints available for three trophic levels: algae, daphnia and fish)

EC₁₀ for *Daphnia magna* has been used for this calculation since it is the most sensitive of the tested species.

Environmental Risk Classification (PEC/PNEC ratio)

PEC/PNEC = 0.245 µg/L / 887 µg/L = 0.00028, i.e. PEC/PNEC ≤ 0.1, which justifies the phrase "Use of valproic acid has been considered to result in insignificant environmental risk".

Biodegradation

Ready biodegradability:

Test showed 48 % degradation in 28 days.

(OECD 301)

(Ref VII)

Justification of chosen degradation phrase:

Valproic acid fails to pass the criteria for ready biodegradability. The phrase "*Valproic acid is potentially persistent*" is thus chosen.

Bioaccumulation

Partition coefficient

$\text{Log } K_{ow} = 2.60$ at pH 7

(OECD 107)

(Ref VIII)

Justification of chosen bioaccumulation phrase:

Since $\text{log } K_{ow} < 4$ at pH 7, valproic acid has low potential for bioaccumulation.

Excretion (metabolism)

Most drug is metabolized to glucuronide conjugates (30-50 %) of the parent drug or of metabolites. Another large portion is metabolized through mitochondrial β -oxidation (40 %). The remainder of metabolism (15-20 %) occurs through oxidation, hydroxylation, and dehydrogenation.

Most drug is eliminated through hepatic metabolism, about 30-50 %. The other major contributing pathway is mitochondrial β -oxidation, about 40 %. Other oxidative pathways make up an additional 15-20 %. Less than 3 % is excreted unchanged in the urine.

(Ref IX).

References

- I. ECHA, European Chemicals Agency, 2008 Guidance on information requirements and chemical safety assessment .
<https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety->
- II. Sanofi, Internal Report: Growth inhibition test with Sodium Valproate on Algae (*Pseudokirchneriella subcapitata*). OECD 201. Report # 11/157-022AL, March 2012.
- III. Sanofi, Internal Report: Acute immobilization test with Sodium Valproate on *Daphnia* (*Daphnia magna*). OECD 202. Report #11/157-023DA, March 2012
- IV. ECHA, registration dossier on 2-propylvaleric acid, Long-term toxicity to aquatic invertebrates, Read across on Sodium Valproate. Available on (2021-08-24):
<https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14340/6/2/5>
- V. Sanofi, Internal report: Sodium Valproate: Fish Embryo Acute toxicity (FET) test. OECD 236. Report # 3200886, April 2015
- VI. ECHA, registration dossier on 2-propylvaleric acid, Long-term toxicity to fish, Read across on Sodium Valproate. Available on (2021-08-24):
<https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14340/6/2/5>
- VII. Sanofi, Internal Report: Determination of the ready biodegradability CO2 evolution test. OECD 301B. Report # 32153 ECS, February 2007

- VIII. Henczi, M., Nagy, J., Weaver, D.F., 1995. Determination of Octanol-water Partition Coefficients by an HPLC method for Anticonvulsant Structure-activity studies. *Journal of Pharmacy and Pharmacology*. 47, 345-347.
- IX. Drug Bank - Valproic acid - retrieved from [drugbank.com](https://www.drugbank.com) 2021-08-24, find here.