FASS

Ergenyl Retard

M

Sanofi AB

Depotgranulat i dospåse 1000 mg

Avregistreringsdatum: 2016-11-02 (Tillhandahålls ej) (Benvitt till svagt gult granulat / utan smak)

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:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.5*10^{-6}*A*(100-R)$

PEC = 0.245 µg/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 = $9*10^6$
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):
EC_{50} 72 h (biomass) = >100 000 µg/L
EC_{50} 72 h (growth rate) = >100 000 µg/L
NOEC = 100 000 µg/L
(OECD 201)
(Ref II)

Crustacean (Daphnia magna):
EC_{50} 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, EC_{50}, EC_{10} 21 d (reproduction) ≥ 8870 µg/L
(OECD 211)
(Ref IV)

Fish (Danio rerio):
LC_{50} 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 EC_{10} or NOEC/10 (Assessment factor justification: three long-term toxicity endpoints available for three trophic levels: algae, daphnia and fish)

EC_{10} 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
Log K_{ow} = 2.60 at pH 7
(OECD 107)
(Ref VIII)

Justification of chosen bioaccumulation phrase:
Since 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 2021-08-24, find here.