

## Anervan<sup>®</sup>

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### Recip AB

Suppositorium

Avregistreringsdatum: 2007-02-28 (Tillhandahålls ej) (Vit, spolformad suppositorie)

Medel mot migrän

### Aktiva substanser:

Ergotamin

Klorcyklizin

Koffein

Meprobamat

### ATC-kod:

N02CA72

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

Läs mer om avregistrerade läkemedel

## Miljöpåverkan

### Koffein

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

Nedbrytning: Det kan inte uteslutas att koffein är persistent, då data saknas.

Bioackumulering: Koffein har låg potential att bioackumuleras.

## Detaljerad miljöinformation

### Environmental Risk Classification

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

PEC is calculated according to the following formula:

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

$$PEC = 1,10 \mu\text{g/L}$$

Where:

A = 7340,6845 kg (total amount API of caffeine and caffeine citrate in Sweden year 2017, data from IQVIA). (Ref. 1)

R = removal rate = 0% (no data available)

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

V (L/day) = volume of waste water per capita and day = 200 (ECHA default) (Ref. 2)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. 2)

### Ecotoxicological studies

Green algae (*Scenedesmus subspicatus*) (ref. 3)

EC<sub>50</sub> 72 hours (reproduction): > 100 mg/L (OECD 201)

Crustacean (*Daphnia magna*) (ref. 4)

EC<sub>50</sub> 24 hours (immobility): 684 mg/L (OECD, 1980, (slightly modified))

Crustacean (*Daphnia magna*) (ref. 5)

EC<sub>50</sub> 48 hours (immobility): 160 mg/L (OECD, 1984)

Crustacean (*Ceriodaphnia dubia*) (ref. 6)

LC<sub>50</sub> 48 hours: 57 mg/L (USEPA, 2002a, static)

LC<sub>50</sub> 7 days: 47 mg/L (USEPA, 2002a, static-renewal)

IC<sub>50</sub> 7 days (reproduction): 44 mg/L (USEPA, 2002a, static-renewal)

IC<sub>25</sub> 7 days (reproduction): 40 mg/L (USEPA, 2002a, static-renewal)

Freshwater fish (*Pimephales promelas*) (ref. 6)

LC<sub>50</sub> 48 hours: 97 mg/L (USEPA, 2002a, static)

LC<sub>50</sub> 7 days: 57 mg/L (USEPA, 2002a, static-renewal, slightly modified)

IC<sub>50</sub> 7 days (growth): 71 mg/L (USEPA, 2002a, static-renewal, slightly modified)

IC<sub>25</sub> 7 days (growth): 50 mg/L (USEPA, 2002a, static-renewal, slightly modified)

For the calculation of PNEC, ecotoxicological data for the most sensitive species, *Ceriodaphnia dubia*, is used. Since no NOEC is available, the long-term IC<sub>25</sub> is used. An assessment factor (AF) of 1000 is applied, in accordance with the ECHA guideline (Ref. 2 chapter R.10).

PNEC is calculated as  $IC_{25}(\text{Ceriodaphnia dubia})/1000$  (AF)

$$\text{PNEC} = 40 \mu\text{g/L}$$

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

$$\text{PEC/PNEC} = 0,028$$

PEC/PNEC < 0,1 which justifies the phrase “Use of Caffeine has been considered to result in insignificant environmental risk”.

### **Degradation**

Concerning biodegradation there is only a not valid study available for caffeine. However, for the structurally analogous compound theophylline there is a test on ready biodegradability available from which it can be concluded that this substance is readily biodegradable (OECD 301 A, 90-100% after 22 days, >90% at the end of the 10-day window). As the two substances differ only by one methyl group it can be concluded with high probability that also the substance caffeine is readily biodegradable. (Ref. 3)

Available degradation data are not sufficient to determine degradability for caffeine in accordance with the FASS guideline, and caffeine is assigned the phrase “The potential for persistence of caffeine cannot be excluded, due to lack of data”.

### **Bioaccumulation**

An experimentally derived  $\text{Log } K_{ow}$  of -0,07 (unknown method) (Ref. 7) indicates that Caffeine has low potential for bioaccumulation.

$\text{Log } K_{ow} < 4$  which justifies the phrase “Caffeine has low potential for bioaccumulation”.

### **Excretion (metabolism)**

Caffeine is metabolized almost completely in the liver and caffeine and its metabolites are excreted through the kidneys of which 3 % or less will be unchanged upon urinary excretion. (Ref. 8, 9)

### **References:**

1. Data from IQVIA "Consumption assessment in kg for input to environmental classification - updated 2018 (data 2017)".
2. ECHA, European Chemicals Agency. Guidance on information requirements and chemical safety assessment. Ver 2.1, 2011. [http://echa.europa.eu/documents/10162/13643/information\\_requirement\\_guidance](http://echa.europa.eu/documents/10162/13643/information_requirement_guidance)
3. OECD SIDS (Screening Information Data Set) Initial Assessment Report: Caffeine, Paris 2002, UNEP Publication.
4. Lilius H et al. (1994), Aquatic Toxicology 30 p47-60
5. Calleja MC et al. (1994), Archives of Environmental Contamination and Toxicology 26 p69-78
6. Moore MT et al. (2008), Archives of Environmental Contamination and Toxicology 54 p31-35
7. Hansch C et al. (1994), ChemID+, US National Library of Medicine, National Institutes of Health, <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp>
8. SPC (Summary of Product Characteristics) Treo Brustablett 500mg/50mg, 2018-12-13, FASS.se
9. Thorn CF et al. PharmGKB, Caffeine Pathway Pharmacokinetics, updated 2019-06-27, <https://www.pharmgkb.org/pathway/PA165884757>, Retrieved 2019-08-16.

