

Altermol

 MR_xS F

Orifarm Generics AB

Tablett 500 mg/30 mg

(vit till nästan vit, kapselformad, plan, fasad, odragerad tablett, 17,5 x 7 mm, präglad med "PC2" på ena sidan och med brytskåra på den andra sidan)



Beroendeframkallande medel.

lakttag största försiktighet vid förskrivning av detta läkemedel.
Särskild receptblankett krävs

Analgetikum

Aktiva substanser:

Kodein, vattenfri

Paracetamol

ATC-kod:

N02AJ06

Läkemedel från Orifarm Generics AB omfattas av
Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för kodein, vattenfri är framtagen av företaget BioPhausia för Citodon®, Citodon® forte, Citodon® minor

Miljörisk: Risk för miljöpåverkan av kodein, vattenfri kan inte uteslutas då ekotoxikologiska data saknas.

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

Bioackumulering: Kodein, vattenfri har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is based on following data:

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

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

A (kg/year) = total sold amount API in Sweden year 2016, data from Quintiles IMS.

R (%) = 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 = $9 \cdot 10^6$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref.1)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref.1)

(Note: The factor 10^9 converts the quantity used from kg to μg).

A = 2174,8 kg. The total sold amount of codeine (codeine hydrochloride dehydrate: 0,523468 kg and codeine phosphate hemihydrate 2174,293525 kg) in Sweden year 2016, data from

Quintiles IMS. (Ref.2)

R = 0

$$PEC = 1.5 * 10^{-6} * 2174,8 * (100-0) = 0,3262200 \mu\text{g/L}$$

Predicted No Effect Concentration (PNEC)

The risk of environmental impact of codeine cannot be excluded, since no ecotoxicity data are available.

Degradation

The potential for persistence of codeine cannot be excluded, due to lack of data.

Bioaccumulation

Codeine has an estimated $\log K_{ow} = 1,14$ (method: Experimental octanol-water partition). (Ref.3)

The $\log K_{ow}$ is thus <4 , which indicates that "Codeine has low potential for bioaccumulation".

References

1. ECHA, European Chemicals Agency.
October 2012 Version: 2.1 Guidance on information requirements and chemical safety assessment.
http://guidance.echa.europa.eu/docs/guidance_document/informa
2. Data from Quintiles IMS "Consumption assessment in kg for input to environmental classification - updated 2017".
3. Sangster, J. Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry, Wiley & Sons: Chichester, 1997.

Miljöinformationen för paracetamol är framtagen av företaget GlaxoSmithKline Consumer Healthcare AB för Alvedon®, Alvedon® Dos, Alvedon® forte, Curadon®, Curadon® forte

Miljörisk: Användning av paracetamol har bedömts medföra låg risk för miljöpåverkan.

Nedbrytning: Paracetamol bryts ned långsamt i miljön.

Bioackumulering: Paracetamol har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.5 \cdot 10^{-6} \cdot 0.85 \cdot A \cdot (100 - 98)$$

$$\text{PEC} = 1.66 \mu\text{g/L}$$

Where:

A = 651683.31 kg (total sold amount API in Sweden year 2016, data from Quintiles IMS). 85% excreted unchanged or as conjugates with potency assumed equal to parent, based on metabolism data (Reference 4). No metabolism has been assumed in the PEC calculation.

R = 98% removal rate from waste water treatment plant (Reference 9)

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

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Reference 1)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Reference 1)

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Green Algae (Scenedesmus subspicatus):

IC50 72h (growth) = 134,000 $\mu\text{g/L}$ (OECD 201) (Reference 5)

Water flea (Daphnia magna):

Acute toxicity

EC50 48 h (immobility) = 9,200 $\mu\text{g/L}$ (OECD 202) (Reference 7)

Zebra Fish (Brachydanio rerio):

Acute toxicity

LC50 96 h (lethality) = 378,000 $\mu\text{g/L}$ (OECD 203) (Reference 5)

Water flea (Daphnia magna):

Chronic toxicity

NOEC 21 days (reproduction) = 1,000 $\mu\text{g/L}$ (OECD 211) (Reference 10)

Fathead minnow (Pimephales promelas):

Chronic toxicity

NOEC (survival) = 460 $\mu\text{g/L}$ (OECD 210) (Reference 11)

Microorganisms in activated sludge

EC50 3 hours (Inhibition) > 1,000,000 $\mu\text{g/L}$ (OECD 209) (Reference 12)

$\text{PNEC} = 460/10 = 0.036 \mu\text{g/L}$

PNEC ($\mu\text{g/L}$) = lowest NOEC/10, where 10 is the assessment factor applied for three chronic NOECs.. The NOEC for Fathead minnow (= 460 $\mu\text{g/L}$) 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 = 1.66/46 = 0.036, i.e. PEC/PNEC \leq 1 which justifies the phrase "Use of paracetamol has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Inherent degradability:

99% degradation in 5 days (OECD 302B) (Reference 3)

Simulation studies:

WWTP study:

Biodegradation constant = 58-80 $\text{L g}_{\text{SS}}^{-1} \text{d}^{-1}$ (Reference 6)

Water-sediment study:

50% (DT50) degradation in 3.10 days (OECD 308) (Reference 8)

Abiotic degradation

Hydrolysis:

Half-life, pH 7 > 1 year (TAD 3.09) (Reference 4)

Photolysis:

No Data

Justification of chosen degradation phrase:

Results of biological degradation: Inherent biodegradation = 99% in 5 days (OECD 302B, IUCLID data set). The substance is inherently biodegradable. The material is expected to be highly removed in wastewater treatment plants, 98% removal (Reference 9). This is supported by a measured biodegradation constant of $58-80 \text{ L g}^{-1}_{\text{ss}} \text{ d}^{-1}$ in a WWTP simulation test (Reference 6).

Biodegradation constants greater than 10 are expected to result in greater than 90% biodegradation. Additionally, a DT50 of 3.1d and a DT90 of 10d was measured (Reference 8) using a water-sediment study (OECD 308) indicating a low potential for persistence. The phrase 'Paracetamol is slowly degraded in the environment' is thus chosen.

Bioaccumulation

Partitioning coefficient:

Log Pow = 0.51 at pH 7 (OECD 107) (Reference 3)

Justification of chosen bioaccumulation phrase:

Since log Pow < 4, the substance has low potential for bioaccumulation.

Excretion (metabolism)

85% of the dose is excreted in urine within 24 hrs as free and conjugated paracetamol (Reference 4). For purposes of the risk assessment assume conjugates are converted back into free paracetamol (Reference 2).

PBT/vPvB assessment

Paracetamol does not fulfil the criteria for PBT and/or vBvP.

All three properties, i.e. 'P', 'B' and 'T' are required in order to classify a compound as PBT (Reference 1). Paracetamol does not fulfil the criteria for PBT and/or vBvP based on a log Dow < 4.

Please, also see Safety data sheets on <http://www.msds-gsk.com/ExtMSDSlist.asp>.

References

1. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
2. Pharmacokinetic properties: Metabolism and Elimination. Summary of Product Characteristics Ziagen (Paracetamol) 300mg Film Coated Tablets. ViiV Healthcare UK Ltd., March 2013.
3. European Chemicals Bureau 2000. IUCLID Dataset Paracetamol.
4. AHFS Drug Information, 2002. American Society of Health-System Pharmacists.
5. Henschel, K., Wenzel, A., Diedrich, M., Fliedner, A. 1997. Regulatory Toxicology and Pharmacology 25, 220-225.
6. Joss, A., et al. 2006. Water Research 40, 1686-1696.
7. Kuhn, R., Pattard, M., Pernak, K.D., Winter, A. 1989. Water Research 23, No.4, 495-499.
8. Loffler, D., Rombke, J., Meller, M., Ternes, T. 2005. Environmental Science and Technology 39, 5209-5218.
9. Ternes, T. 1998. Water Research 32, No.11 3245-3260.
10. [Smithers Viscient AG Study No. 1162.000.230]
4-Hydroxyacetanilide: Chronic reproduction test with daphnids (Daphnia magna) under semi-static conditions OECD No. 211, Dated August 11, 2011.

- 11.** [Smithers Viscient AG Study No. 1162.000.122]
4'-Hydroxyacetanilide: Early life-stage toxicity test with fathead minnow (*Pimephales promelas*) under flow-through conditions, OECD 210, Dated October 14, 2011.
- 12.** [Smithers Viscient AG Study No. 1162.000.790]
4'-Hydroxyacetanilide: Activated sludge respiration inhibition test, OECD # 209, Dated August 8, 2011