

## Dolerin

MR F<sub>f</sub>

Karo Pharma

Filmdragerad tablett 500 mg/150 mg

(Vita, kapselformade, filmdragerade tabletter, längd 19 mm, brytskåra på ena sidan och släta på den andra sidan.)

Paracetamol, kombinationer exkl. neuroleptika

### Aktiva substanser:

Ibuprofen

Paracetamol

### ATC-kod:

N02BE51

Läkemedel från Karo Pharma omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

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:

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

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

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 µg/L (OECD 201) (Reference 5)

*Water flea (Daphnia magna):*

Acute toxicity

EC50 48 h (immobility) = 9,200 µg/L (OECD 202) (Reference 7)

*Zebra Fish (Brachydanio rerio):*

Acute toxicity

LC50 96 h (lethality) = 378,000 µg/L (OECD 203) (Reference 5)

*Water flea (Daphnia magna):*

Chronic toxicity

NOEC 21 days (reproduction) = 1,000 µg/L (OECD 211) (Reference 10)

*Fathead minnow (Pimephales promelas):*

Chronic toxicity

NOEC (survival) = 460 µg/L (OECD 210) (Reference 11)

Microorganisms in activated sludge

EC50 3 hours (Inhibition) > 1,000,000 µg/L (OECD 209) (Reference 12)

PNEC =  $460/10 = 0.036$  µg/L

*PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three chronic NOECs.. The NOEC for Fathead minnow (= 460 µg/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 =  $58-80 \text{ L g}^{-1}_{\text{ss}} \text{ d}^{-1}$  (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 L g<sup>-1</sup> d<sup>-1</sup> 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**

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4. AHFS Drug Information, 2002. American Society of Health-System Pharmacists.
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6. Joss, A., et al. 2006. Water Research 40, 1686-1696.
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10. [Smithers Visient 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