

## Tiplo Citrus

M EF

### Orifarm Generics AB

Brustablett 500 mg/50 mg

(Vit till benvit runda, plana Brustabletter med ojämn fördelade gula prickar (diameter 20 mm, tjocklek 5,2 mm))

Lätta analgetika och antipyretika

### Aktiva substanser:

Acetylsalicylsyra

Koffein

### ATC-kod:

N02BA51

Läkemedel från Orifarm Generics AB omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

Miljöinformationen för acetylsalicylsyra är framtagen av företaget Bayer för Alka-Seltzer®, Aperyl, Aspirin, Aspirin Cardio, Aspirin®, Chinaspin, Dolviran, Dolviran N, Instantine, Spasmo-dolviran

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

Nedbrytning: Acetylsalicylsyra bryts ned i miljön.

Bioackumulering: Acetylsalicylsyra har låg potential att bioackumuleras.

### Detaljerad miljöinformation

#### Environmental Risk Classification

#### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$PEC = 19,508 \mu\text{g/L}$$

Where:

**A = 130053,307 kg** (total sold amount API in Sweden year 2016, data from QuintilesIMS).

R = 0 % 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 (1))

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

### **Predicted No Effect Concentration (PNEC)**

#### **Ecotoxicological studies**

*Algae (Desmodesmus subspicatus):*

NOEC/72 h (growth inhibition, growth rate) 14180 µg/L (guideline OECD 201) (2)

*Crustacean (waterflea Daphnia magna):*

Chronic toxicity

NOEC/21 days (reproduction, mortality)  $\geq 1000$  µg/L (guideline OECD 211) (3)

*Fish:*

Chronic toxicity

NOEC 30 days (growth) = 283 µg/L, LOEC 834 µg/L (ELS test, guideline OECD 210) (4)

*Microorganisms (activated sludge, respiration inhibition):*

NOEC/30 min > 100000 µg/L (nominal) (guideline OECD 209) (5)

PNEC = 28,3 µg/L (Lowest chronic NOEC fish = 283 µg/L; AF 10)

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

PEC/PNEC ratio:  $19.508/28,3 = 0.69$ , i.e.  $0,1 < PEC/PNEC \leq 1$  which justifies the phrase *Use of acetylsalicylic acid has been considered to result in low environmental risk.*

### **Degradation**

#### **Biotic degradation**

*Ready degradability:* Readily biodegradable

Acetylsalicylic acid was studied for aerobic biodegradability in water in a manometric respiration test according to guideline OECD 301F (6). The substance was introduced into the test system at a concentration of 200 mg/L as theoretical oxygen demand (ThOD) and was found to be degraded to 69.6% after 10 and 83.3 % after 28 days. Hence, acetylsalicylic acid can be regarded as readily biodegradable. The results of the study on ready biodegradability justifies the phrase *Acetylsalicylic acid is degraded in the environment.*

#### **Abiotic degradation**

*Hydrolysis:*

Acetylsalicylic acid is known to hydrolyze in contact with moisture yielding acetic acid and salicylic acid. In basic solutions acetylsalicylic acid hydrolyzes rapidly, and the half-life decreases with increasing pH (7).

#### **Bioaccumulation**

*Partitioning coefficient:*

A study on the n-octanol/water partition coefficient was conducted according to OECD 107 (8). The log  $K_{OW}$  at 20 °C was - 0.32, - 1.62, and - 1.61 at pH 5, 7 and 9, respectively. The negative log  $K_{OW}$  indicated an insignificant lipophilicity and hence, a lack of a bioaccumulation potential.

Since the log  $P_{OW}$  (at pH 7) is -1.62, the phrase *Acetylsalicylic acid has a low potential for bioaccumulation* is justified.

#### **Excretion (metabolism)**

In human body acetylsalicylic acid is deacetylated to salicylic acid and then further metabolized. It is predominantly excreted via urine as salicylic acid and subsequent salicylate metabolites salicyluric acid

(glycine conjugate), salicyl phenolic glucuronide, salicyl acyl glucuronide, gentisic acid (oxidation product), gentisuric acid (glycine conjugate) and to a lesser extent in the unmetabolized form as parent compound (9). However, the acetylsalicylic acid metabolism in humans and therefore the proportions of the excreted urine metabolites significantly vary inter-individually depending on urine pH, sex, ethnicity, and variants in metabolizing enzymes (10).

## References

- (1) ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
- (2) Growth inhibition test of BAY e4465 (Acetylsalicylic acid) with *Desmodesmus subspicatus*. Nonclinical Drug Safety, Bayer Schering AG, study no. T100981-9, report no. PH-38090 (2014)
- (3) Reproduction study of BAY e4465 (Acetylsalicylic acid) in *Daphnia magna*. Nonclinical Drug Safety, Bayer Schering AG Study no. T100979-6, report no. PH-38263 (2014)
- (4) ASS 180/840 KG Early-life-stage test with Zebrafish (*Danio rerio*) under Flow-Through Conditions). Nonclinical Drug Safety, Bayer Schering AG Study no. T100876-2, report no. R-9373 (2014)
- (5) Respiration inhibition test with BAY e4465 (Acetylsalicylic acid) on activated sludge microorganisms. Nonclinical Drug Safety, Bayer Pharma AG, study no T101029-3, report no. PH-3898 (2014)
- (6) Study on the biodegradability of BAY e4465 (Acetylsalicylic acid) in the manometric respiration test. Nonclinical Drug Safety, Bayer Schering Pharma AG, study no T101073-2, report no. PH-37791 (2014)
- (7) Mitchell AG, Broadhead JF. Hydrolysis of solubilized aspirin. *J Pharm Sci.* 1967, 56(10):1261-6.
- (8) BAY e 4465: Determination of the partition coefficient (n-octanol/water) by the shake-flask method at different pH values. Nonclinical Drug Safety, Bayer Pharma AG, study no T101857-2, report no. R-9744 (2016)
- (9) Jjemba PK. Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. *Ecotoxicology and Environmental Safety*, 2006; 63(1): 113-130.
- (10) Navarro SL, Saracino MR, Makar KW, Sushma TS, Li L, Zheng Y, Levy L, Schwarz Y, Bigler J, Potter JD, Lampe JW. Determinants of aspirin metabolism in healthy men and women: effects of dietary inducers of UDP-glucuronosyltransferases. *J Nutrigenet Nutrigenomics*, 2011; 4(2): 110-118.