

**Cozaar®**

**MR EF**

**MSD**

Filmdragerad tablett 50 mg

(vit, oval, längd 10,3 mm, bredd 5,6 mm, ena sidan märkt 952, den andra sidan skårad)

Angiotensin II-antagonist

**Aktiv substans:**

Losartan

**ATC-kod:**

C09CA01

Läkemedel från MSD omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Losartan

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

Nedbrytning: Losartan är potentiellt persistent.

Bioackumulering: Losartan har låg potential att bioackumuleras.

### Detaljerad miljöinformation

#### Environmental Risk Classification

#### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 1.2 \mu\text{g/L}$$

Where:

A = 8161 kg (total sold amount API in Sweden year 2015, data from IMS Health).

R = 0 % removal rate (worst case assumption)

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

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

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

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

#### **Ecotoxicological studies**

*Green Algae (Selenastrum capricornutum)* (FDA 4.01) (Ref. II):

NOEC 10 day (cell growth) = 143 mg/L

*Blue Green Algae (Microcystis aeruginosa)*(FDA 4.01) (Ref. III): NOEC 10 day (cell growth) = 556 mg/L

*Crustacean, water flea (Daphnia magna)*:

Acute toxicity

LC<sub>50</sub> 48 h (mortality) = 331 mg/L (OECD 202) (Ref.IV)

NOEC = 80 mg/L

Chronic toxicity

NOEC 21 day (survival, reproduction, growth) = 100 mg/L (OECD 211) (Ref V)

No effects noted up to the highest concentration tested

*Fish, fathead minnow (Pimephales promelas)*:

Acute toxicity

LC<sub>50</sub> 48 h (mortality) > 1000 mg/L (U.S. EPA "Methods for Measuring the Acute Toxicity of Effluents to Fresh Water and Marine Organisms", 1985) (Ref.IV)

NOEC = 100 mg/L

Chronic toxicity

NOEC 32-day (survival, hatching, growth) = 10 mg/L (OECD 210) (Ref VI)

No effects noted up to the highest concentration tested

*Fish, rainbow trout (Oncorhynchus mykiss)*:

Acute toxicity

LC<sub>50</sub> 96 h (mortality) > 929 mg/L (FDA 4.11) (Ref.VII)

NOEC = 929 mg/L

PNEC = 1000 µg/L (10000 µg/L/ 10 based on the most sensitive chronic NOEC for the fish with an assessment factor (AF) of 10)

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

PEC/PNEC =  $1.2/1000 = 0.001$ , i.e.  $PEC/PNEC \leq .1$  which justifies the phrase "Use of losartan has been considered to result in insignificant environmental risk."

#### **Degradation**

##### **Biotic degradation**

Bacteria > 90% of initial concentration remaining

Algal = 71% of initial concentration remaining after 28 days (FDA 3.11). (Ref VIII)

### **Abiotic degradation**

#### *Hydrolysis:*

Hydrolytically stable between pH 5-9 (FDA 3.09). (Ref. IX)

#### *Photolysis:*

Susceptible to aqueous photolysis and rapidly degrades under clear sky conditions

Half-Life<sub>max</sub> < 18 hours (pH 9) over wavelength interval 290-800 nm

(FDA 3.10). (Ref. X)

#### *Justification of chosen degradation phrase:*

Losartan has been found to degrade under natural light conditions however no data are available on metabolites. Therefore the phrase "Losartan is potentially persistent" was thus chosen.

### **Bioaccumulation**

#### *Partitioning coefficient:*

Log K<sub>ow</sub> = 1.2 (OECD 107). (Ref.XI)

#### *Justification of chosen bioaccumulation phrase:*

Since log K<sub>ow</sub> < 4 at pH 7, the substance has low potential for bioaccumulation

### **References**

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[http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
- II. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Toxicity to the Freshwater Green Alga, Selenastrum capricornutum, Under Static Test Conditions," Study No., J9209001f, TOX, Jupiter, FL, USA, 16 June 1993.
- III. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Toxicity to the Blue-Green Alga, Microcystis aeruginosa, Under Static Test Conditions," Study No., J9209001g, TOX, Jupiter, FL, USA, 16 June 1993.
- IV. Merck, 1995. "Environmental Quality Criteria Monograph for Losartan Potassium", Merck & Co., Inc. Whitehouse Station, NJ, USA, 24 November 1995.
- V. Smithers Visicent, 2013. "Losartan - Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static Renewal Conditions Following OECD Guideline #211" Smithers Visicent Study Number 359.6707" Wareham, MA, USA, 18 June 2013.
- VI. Smithers Visicent, 2013. "Losartan - Early Life-Stage Toxicity Test with Fathead Minnow, Pimephales promelas, Following OECD Guideline #210" Smithers Visicent Study Number 359.6706" Wareham, MA, USA, 10 June 2013.
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- X. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Determination of Aqueous Photolysis," Study No., J9209001c, TOX, Jupiter, FL, USA, 02 July 1993.
- XI. Merck & Co., Inc., 1995 "New Drug Application for Tablets Losartan Potassium, Environmental Assessment, Feb 1 1995"