

Cozaar[®]

M R EF

Organon Sweden

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 Organon Sweden omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Losartan

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

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

Bioackumulering: Losartan har låg potential att bioackumuleras.

Detaljerad miljöinformation

Losartan potassium is an angiotensin II receptor (AT1) antagonist that mediates the vasoconstricting activity of angiotensin II in vascular smooth muscle and aldosterone secreting effects of the adrenal gland. It is used alone or with other blood pressure medicines to lower high blood pressure (hypertension), to lower the chance of stroke in patients with high blood pressure and a heart problem called left ventricular hypertrophy and to slow the worsening of diabetic kidney disease (nephropathy) in patients with type 2 diabetes who have or had high blood pressure.

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

$$\text{PEC} = 1.487 \mu\text{g/L}$$

Where:

A = 10854.72 kg (total sold amount API in Sweden year 2021, data from IQVIA). *Reduction of A may be justified based on metabolism data.*

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is

available. (If $R \neq 0$ this should be justified under the degradation section)

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

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

D = factor for dilution of wastewater 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

LC50 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 IV)

No effects noted up to the highest concentration tested

Flathead Minnow (*Pimephales promelas*) (Ref V)

Acute toxicity

LC50 48 h (mortality) = >1000 mg/L

No effects noted up to the highest concentration tested

Chronic toxicity

NOEC 32-day > 10 mg/L

No effects noted up to the highest concentration tested

Fish, rainbow trout (*Oncorhynchus mykiss*):

Acute toxicity

LC50 96 h (mortality) > 929 mg/L (FDA 4.11) (Ref.VI)

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 = 1.487/1000 = , i.e. PEC/PNEC ≤ 0.0014

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 VII)

Abiotic degradation

Hydrolysis:

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

Photolysis:

Susceptible to aqueous photolysis and rapidly degrades under clear sky conditions Half-Lifemax < 18 hours (pH 9) over wavelength interval 290-800 nm (FDA 3.10). (Ref. IX)

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 Kow = 1.2 (OECD 107). (Ref. XI)

Justification of chosen bioaccumulation phrase:

Since log Kow < 4 at pH 7, the substance has low potential for bioaccumulation

References

- I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/informa
- 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. 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.
- V. 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.
- VI. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Acute Toxicity to Rainbow Trout, *Oncorhynchus mykss*, Under Static Test Conditions," Study No., J9209001i, TOX, Jupiter, FL, USA, 28 May 1993.
- VII. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Biodegradation Inoculum Source Screening and Aerobic Biodegradation in Water," Study No., J9209001d, TOX, Jupiter, FL, USA, 06 August 1993.
- VIII. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Determination of the Rate of Hydrolysis as a Function of pH," Study No., J9209001b, TOX, Jupiter, FL, USA, 02 March 1993.
- IX. Toxikon Environmental Sciences, 1993. "Losartan (MK-0954): Determination of Aqueous Photolysis," Study No., J9209001c, TOX, Jupiter, FL, USA, 02 July 1993
- 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"