

Atozet

M R (F)

Organon Sweden

Filmdragerad tablett 10 mg/80 mg

(kapselformade, bikonvexa, vita till benvita filmdragerade tabletter, 19,05 mm x 7,94 mm, märkta med "357" på en sida)

HMG-CoA-reduktashämmare i kombination med andra lipidmodifierande medel

Aktiva substanser (i bokstavsordning):

Atorvastatin

Ezetimib

ATC-kod:

C10BA05

Läkemedel från Organon Sweden omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Atorvastatin

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

Nedbrytning: Atorvastatin bryts ned i miljön.

Bioackumulering: Atorvastatin har låg potential att bioackumuleras.

Detaljerad miljöinformation

Atorvastatin is synthetic lip-lowering agent used for treatment of high cholesterol. Studies of at atorvastatin indicate it is soluble in water (327 mg/l) at 20 C. (Ref II)

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A(100 - R)$$
$$\text{PEC} = 0.0011 \text{ mg/L}$$

Where:

A = 8141.9479 kg (total sold amount API in Sweden year 2022, 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 not = 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 waste water by surface water flow = 10 (ECHA default) (Ref. I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

Algae (Pseudokirchneriella subcapitata) (guideline eg OECD 201) (Reference VI):

NOEC (growth) = 14 mg/L

Crustacean (Daphania magna):

Acute toxicity

EC_{50} 48 h (immobility) = 200 mg/L (guideline eg OECD 202)

(Reference IX)

Chronic toxicity

NOEC 21 days (growth) = 0.20 mg/L (guideline eg OECD 211) (Reference XI)

Fish (Pimephalse promelas):

Acute toxicity

LC_{50} 96 h (mortality) = <92 mg/L (guideline eg OECD 203)

(Reference IX)

Chronic toxicity

NOEC 33 days (growth) = 0.49 g/L (guideline eg OECD 210) (Reference X)

An PNEC of 0.02 mg/L was determined for atorvastatin based on the results of the chronic water flea study, the most sensitive species tested (NOEC = 0.2 mg/L) An assessment (safety) factor of 10 (AF = 10) was applied since sufficient chronic toxicity data is available for species from three trophic levels.

Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 0.0011/0.02 = 0.055$, i.e.

‘Use of atorvastatin has been considered to result in insignificant environmental risk.’

Degradation*

Studies of atorvastatin indicate it is soluble in water (327 mg/L) at 20°C. Studies of the octanol-water partition coefficient (K_{ow}) indicate that atorvastatin does not have the potential to bioaccumulate in organisms ($\log K_{ow} = 1.62$ at pH 7). The $\log K_{oc}$ values indicate it is mobile in soil and sludge ($\log K_{oc} < 3$). A biodegradation study indicates that atorvastatin is rapidly biodegradable in sludge. (Ref. III-IV, VI)

Primary degradation (Loss of parent):

Half-life (DT50) in water = 19.9 to 21.9 days

DT50 in total system = 26.4 to 32.4 days. (Ref. V)

The amounts of Atorvastatin in the total test systems (i.e. water layers plus sediment extracts) at the end of the test were 7.8% and 3.3%, respectively. The DT50 values for parent Atorvastatin in the total test systems were 32.4 and 26.4 days.

A measured portion (25 mL) of extraction solvent was added to each vial. The extraction solvent was acetone/tetrahydrofuran (1:1), the same solvent used to extract sediment samples. Sediment samples were fortified with [¹⁴C]Atorvastatin and extracted using a variety of solvents. The extraction solvent that provided the best results was a mixture of acetone and tetrahydrofuran (ACE/THF 1:1).

Bioaccumulation

Partitioning coefficient:

log K_{ow} pH 5 = 3.38

pH 7 = 1.62

pH 9 = 0.745 (guideline eg OECD 107). (Reference IV)

Since log D_{ow} < 4 at pH 7, the substance has low potential for bioaccumulation.

References

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- IV. Wildlife International, 2010. "Determination n-octanol/water partition coefficient by the shake flask method" OECD 107, Project number 105C-143. 1 March 2010.

- V. Wildlife International, 2011. " Atorvastatin: Aerobic Transformation in Aquatic Sediment Systems," OECD 308 Project No., 105E-154, 2 September 2011.
- VI. Wildlife International, 2011. "Atorvastatin: Biodegradation in Activated Sludge: OECD 314B, Project number 105E-155. 11 March 2011.
- VII. Wildlife International, 2010. "Atorvastatin: A 96-hr toxicity test with the freshwater alga (*Pseudokirchneriella subcapitata*)", OECD 201, Project No. 105A-194, 9 April 2010.
- VIII. Wildlife International, 2010. "Atorvastatin: An Activated Sludge, Respiration Inhibition Test" OECD 209, Project number 105E-151. 13 January 2010.
- IX. Pfizer, 2013. LIPITOR Safety Data Sheet, accessed from http://www.pfizer.com/sites/default/files/products/material_safety_ on 22 August 2014.
- X. Wildlife International, 2010. "Atorvastatin: An early life-stage toxicity test with the fathead minnow (*Pimephales promelas*)", OECD 210, Project No. 105A-196, 7 September 2010.
- XI. Wildlife International, 2010. "Atorvastatin: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*)", OECD 211, Project No. 105A-195, 8 July 2010.
- XII. Wildlife International, 2012. "14C-Atorvastatin: A Prolonged Sediment Toxicity Test with *Chironomus riparius* using spiked sediment" Project No., 105A-202A, 13 July 2012.

Ezetimib

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

Nedbrytning: Ezetimib är potentiellt persistent.

Bioackumulering: Ezetimib har låg potential att bioackumuleras.

Detaljerad miljöinformation

Detailed background information

Studies of ezetimibe indicate it is poorly soluble in water (0.5 mg/L). Adsorption/desorption studies indicate ezetimibe is likely to bind to soils and sludge to some degree (log K_{oc} range 3.6 to 4.4). The high octanol/water partition coefficient (log K_{ow} > 4) suggested the potential to bioaccumulate in aquatic organisms, however measured bioconcentration factors in bluegill sunfish ranged from 69 to 173, indicating a low potential for bioaccumulation [Ref X].

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.053 \mu\text{g/L}$$

Where:

A = 386.55 kg (total sold amount API in Sweden year 2022, 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 not equal to 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 waste water by surface water flow = 10 (ECHA default) (Ref. I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

Green Algae (*Selenastrum capricornutum*) (OECD 201) (Ref. II):

EC50 72 h (density) = >0.3 mg/L

EC50 72 h (growth rate) = >0.3 mg/L

NOEC 72 h = 0.3 mg/L

Non-toxic up to highest concentration tested

Crustacean, water flea (*Daphnia magna*):

Acute toxicity

LC50 48 h (mortality) > 4 mg/L (OECD 202) (Ref. III)

Non-toxic up to highest concentration tested

Chronic toxicity

NOEC 21 day (mortality; reproduction) = 0.3 mg/L (OECD 211) (Ref. IV)

Non-toxic up to highest concentration tested

Fish, fathead minnow (*Pimephales promelas*):

Acute toxicity

LC50 96 h (mortality) > 0.13 mg/L (OECD 203) (Ref. V)

Non-toxic up to highest concentration tested

Chronic toxicity

NOEC 33 days (growth, total length) = 0.05 mg/L (OECD 210) (Ref. VI)

Midge (*Chironomus riparius*)

Chronic toxicity

NOEC 28 days (growth) = 877mg/kg

While significant shifting of this compound to the sediment is likely to occur, chronic toxicity tests with the midge (*Chironomus riparius*) indicate the compound is non-toxic to sediment dwelling organisms (21-day EC50 > 877 mg/kg, which is the highest concentration tested).(Ref XI)

PNEC (µg/L) = 50/10 = 5 µg/L where 10 is the assessment factor used for three long-term ecotoxicity data endpoints. NOEC for fathead minnow has been used for this calculation since it is the most sensitive of the three tested species.

Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 0.053/5 = 0.011$, i.e. PEC/PNEC ratio < 1 which justifies the phrase 'Use of Ezetimibe has been considered to result in insignificant long-term risk to the environment.'

Degradation*

Biotic degradation

Biodegradation Simulation Screening

Test results 7% biodegradation to CO₂ by Day 28. (OECD 301B) (Ref. VII)

Test results 4% biodegradation to CO₂ by Day 28; 83% biodegradation to metabolites (OECD 314) (Ref. VIII)

Abiotic degradation

Hydrolysis:

Half-life of 4.5 days at pH 7, 25°C (OECD 111) (Ref. IX)

Justification of chosen degradation phrase:

Ezetimibe is inherently degradable in biological systems and via hydrolysis. However, as no data are available on the toxicity of the metabolites, the phrase "Ezetimibe is potentially persistent in the environment" is thus chosen.

Bioaccumulation

Bioconcentration Factor (BCF):

Measured BCF values were 69 (low concentration) and 137 (high concentration) in a 97 day study with bluegill sunfish (OECD 305). (Ref. X)

Justification of chosen bioaccumulation phrase:

Since $BCF < 500$, the substance has low potential for bioaccumulation

References

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