FASS

Inegy®

Organon Sweden

Tablett 10 mg/40 mg

(Vita till benvita, kapselformade tabletter märkta med "313" på en sida.)

Medel som påverkar serumlipidnivåerna, kombinationer

Aktiva substanser (i bokstavsordning):

Ezetimib

Simvastatin

ATC-kod:

C10BA02

Läkemedel från Organon Sweden omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

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 Koc range 3.6 to 4.4) The high octanol/water partition coefficient (log Kow > 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:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A(100-R)$

PEC = 0.053 µg/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 = $10 *10^{6}$

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^{o}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

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
II. Wildlife International, 2009. "Ezetimibe: A 96-hr toxicity test with the freshwater alga (Pseudokirchneriella subcapitata)", OECD 211, Project No. 105A-174, Wildlife International, 2 February 2009.
III. Toxikon Corp., 2001. "JV-AT-A: Acute Toxicity to the water flea, Daphnia magna, under static test conditions" OECD 202 (Part 1), Project ID 01J0006c. Toxicon Corp., 17 October, 2001. August 2013
IV. Wildlife International, 2009. "Ezetimibe: A flow-through life-cycle toxicity test with the cladoceran (Daphnia magna)", OECD 211, Project No. 105A-175, Wildlife International, 26 February 2009.
V. Toxikon Corp., 2001. "JV-AT-A: Acute Toxicity to fathead minnow, Pimephales promelas, under static test conditions" OECD 203, Project ID 01J0006e. Toxicon Corp., 17 October, 2001.
VI. Wildlife International, Ltd., Ezetimibe: an early life-stage toxicity test with the fathead minnow (pimephales promelas), WIL Project Number 105A-176, Easton MD, 17 March 2009.

VII. Toxicon, 2002. "JV-AT-A: Ready Biodegradability: CO2 Evolution (Modified Sturm Test)", Toxicon Report 01J0001, Jupiter Fl, 10 April 2002.
VIII. Wildlife International, 2009. "Ezetimibe dieaway in activated sludge", WIL Project Number 105E-129, Easton MD, 2 Nov 2009.Wildlife International, 2009.
IX. "Ezetimibe: An evaluation of hydrolysis as a function of pH" OECD 111, Project number 105C-121. Wildlife International, 4 May 2009.
X. Wildlife International, 2011. "Ezetimibe: A Bioconcentration Test with the Bluegill (Lepomis macrochirus)," Project No. 105A-197, WIL, Easton, MD, USA, 16 March 2011.
XI. Wildlife International, 2011. "[14C] Ezetimbe: A Prolonged Sediment Toxicity Test with Chironomus riparius usind Spiked Sediment, OECD 218, Project No, 105A-198, 15 April 2011.

Simvastatin

Miljörisk: Användning av simvastatin har bedömts medföra medelhög risk för miljöpåverkan.
Nedbrytning: Det kan inte uteslutas att simvastatin är persistent, då data saknas.
Bioackumulering: Simvastatin har hög potential att bioackumuleras.

Detaljerad miljöinformation

Simvastatin) is a cholesterol-lowering agent intended for use in humans. Simvastatin is a pro-drug of the active pharmaceutical ingredient, simvastatin hydroxy acid, the molecule that inhibits 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase. This enzyme is the rate-limiting step in the biosynthetic pathway responsible for the de novo synthesis of cholesterol in the liver. Patients taking simvastatin (and thereby simvastatin hydroxy acid) are found to significantly reduce the levels of cholesterol in the body. Because simvastatin hydroxy acid (salt form is simvastatin ammonium salt) is the active pharmaceutical ingredient, this assessment focuses on the fate and effects of this molecule. No chronic toxicity studies were conducted, as simvastatin is expected to hydrolyze to simvastatin hydroxy acid within a short time frame. Chronic toxicity was apparent with *D. magna* the most sensitive species base on neonate survival (reproduction endpoint). Although at concentrations unlikely to be seen in the environment, simvastatin ammonium salt was toxic to sediment dwellings midges at 4.4 mg/kg.

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

PEC = 0.3108 µg/L

Where:

A = 2 268.6076 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.

P = number of inhabitants in Sweden = $10*10^{6}$

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 *(Pseudokirchneriella subcapitata)* (guideline eg OECD 201) (Reference VI)*:*
EC_{50} 72 h (growth) = 27.4 (yield) 120 (growth rate) mg/L
EC_{10} or NOEC = 2.45 mg/L

Water flea *(Daphnia magna):*

Acute toxicity
EC_{50} 48 h (mortality) = 3.5 mg/L (guideline eg OECD 202) (Reference IV)

Chronic toxicity
NOEC 21 days (growth, reproduction) = 0.002 mg/L (guideline eg OECD 211) (Reference VIII)
Flathead Minnow *(Pimephales promelas):*

Acute toxicity
LC_{50} 96 h (mortality) = 2.91 mg/L (guideline eg OECD 203) (Reference V)

Chronic toxicity
NOEC 31 days (growth) = 0.008 mg/L (guideline eg OECD 210) (Reference VI)
Midge *(Chironomus riparious)*

Chronic toxicity
NOEC 28 days (growth) = 4.39 mg/kg (Reference IX)
Other ecotoxicity data: PNEC = 0.2 µg/L (justification of chosen assessment factor (AF))
PNEC (µg/L) = 0.002 mg/L /10, where 10 is the assessment factor used for three long-term ecotoxicity data endpoints.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.3108/0.2 = 1.55
A complete set of environmental fate and effects data of the active pharmaceutical, simvastatin hydroxy acid, was collected. Simvastatin and its metabolites have a low risk to the environment from normal patient use.

Degradation*

Biotic degradation

The potential for persistence of simvastatin cannot be excluded, due to lack of data.

Bioaccumulation

Simvastatin hydroxy acid is expected to bioaccumulate due to its measured log octanol water partition coefficient based on OECD 107 [II]
Partitioning coefficient: Log Kow = pH 5 > 4.11
pH 7 > 4.07

pH 9 > 4.07

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

II. Smithers Viscient, 2011. "Simvastatin - Determining the Partition Coefficient (n-Octanol/Water) by the Flask-Shaking Method Following OECD Guideline 107,"Study No., 359.6338, SSL, Wareham, MA, USA, 05 January 2011

III. Smithers Viscient, 2011. "Simvastatin - Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECDGuideline 111," Study No., 359.6337, SSL, Wareham, MA, USA, 17 February 2011.

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V. Merck, 1997. Memo K. Kumke to E. Venkat "Preliminary Environmental QualityCriteria Guidance for Simvastatin", 21 March 1997.

VI. Huntingdon Life Sciences, 2011. "Simvastatin Ammonium Salt Algal GrowthInhibition Assay," Study No. PPM0005, HLS, UK, 19 April 2011

VII. Huntingdon Life Sciences, 2011. "Simvastatin Ammonium Salt Fish Early Life StageToxicity Test for Fathead Minnow," Study No. PPM0007, HLS, UK, 23 Dec 2011

VIII. Huntingdon Life Sciences, 2010. "Simvastatin ammonium salt Daphnia magna reproduction toxicity test" HLS report PPM0006, Huntingdon, Cambridgeshire, England. 12 May 2011.

IX. Huntingdon Life Sciences, 2011. "Simvastatin Ammonium Salt; Toxicity to theSediment-Dwelling Phase of the Midge Chironomus riparius" Study No. PPM0009,HLS, UK, 23 March 2012