FASS

Diovan® Comp

MREF

Novartis

Filmdragerad tablett 320 mg/12,5 mg
(rosa, oval filmdragerad tablett med fasade kanter, märkt med "NVR" på ena sidan och "HIL" på den andra sidan)

Angiotensin II-antagonist och diuretikum

Aktiva substanser:
Hydroklortiazid
Valsartan

ATC-kod:
C09DA03

Läkemedel från Novartis omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Hydroklortiazid

Miljörisk: Användning av hydroklortiazid har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Hydroklortiazid bryts ned långsamt i miljön.
Bioackumulering: Hydroklortiazid har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification
Predicted Environmental Concentration (PEC)
PEC is calculated according to the following formula:
PEC (µg/L) = $(A*10^9*(100-R))/(365*P*V*D*100) = 1.5 * 10^{-6} * A * (100-R)$ = 0.42 µg/L
Where:
A = 2789.28 kg (total sold amount API in Sweden year 2016, data from QuintilesIMS).
R = 0 % removal rate.
P = number of inhabitants in Sweden = $9 *10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Pseudokirchneriella subspicata) (OECD201) (NOTOX Project 490915)*:*
EC50 72 h (growth rate) > 100.0 mg/L
NOEC 72 h = 100.0 mg/L

Crustacean (Daphnia magna, waterflea*):*
Acute toxicity
EC50 48 h (immobilisation) > 100.0 mg/L (OECD202) (Ciba-Geigy Test No: 948032)
Chronic toxicity
NOEC 21 days (reproduction, survival and parental length) = 100 mg/L; no effect up to the highest concentration tested (OECD 211) (NOTOX Project 485928)

Fish:
Acute toxicity (*Danio rerio,* zebra fish)
LC50 96 h (mortality) > 100.0 mg/L (OECD203) (Ciba-Geigy Test No. 811678)
Chronic toxicity (*Pimephales promelas,* fathead minnow)
NOEC 30 days (hatchability, survival, length and weight) = 10.0 mg/L; no effect up to the highest concentration tested (OECD 210) (NOTOX Project 485928)

Other ecotoxicity data:
Bacterial respiration inhibition
EC_{50} 3 h > 750 mg/L (activated sludge respiration inhibition) (OECD209) (Ciba-Geigy Test No. 948033)

Sediment-dwelling organisms (*Chironomus riparius*, non-biting midge)
NOEC 28 days (emergence rate and development rate) = 10.0 mg/L (OECD 218) (Report No BR0137/B)

PNEC derivation:
PNEC = 1000 µg/L
PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for fish early life stage toxicity has been used for this calculation.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.42 µg/L / 1000 µg/L = 0.00042, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of hydrochlorothiazide has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:
36.0 % degradation in 28 days, not readily biodegradable (OECD301E). (Report No. BR0030/B)
Simulation studies:
DT_{50} (total system) = 34.7 – 37.3 days (OECD 308). (Report No. BR0040/B)
Sediments were extracted with 100 ml of methanol by agitating for at least 12 hours. This was followed by a further extraction with 100 ml of 90% ethanol.
A significant amount of mineralisation occurred throughout the study. At the end of the study $^{14}CO_2$ accounted for 58% to 70%. Non-extractable residues in sediment accounted for 9-23% of applied

radioactivity by the end of the study. Parent substance was 10-11 % of applied radioactivity by the end of the study.

Justification of chosen degradation phrase:
According to the pass criteria for OECD308 studies, hydrochlorothiazide can be classified as 'Hydrochlorothiazide is slowly degraded in the environment' (DT_{50} for total system <120days)

Bioaccumulation

Partitioning coefficient:
Log D_{ow} = 0.09 at pH 7 (OECD107). (NOTOX Project 490916)

Justification of chosen bioaccumulation phrase:
Since log Dow < 4 at pH 7, hydrochlorothiazide has low potential for bioaccumulation.

Excretion (metabolism)

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. Within 72 hours, 60-80% of a single oral dose is excreted in the urine, 95% in unchanged form, and about 4% as the hydrolysate 2-amino-4-chloro-m-benzenedisulfonamide (ACBS). Up to 24% of an oral dose may be found in the feces, and a negligible amount is excreted via the bile. (ESIDREX® (hydrochlorothiazide) Core Data Sheet)

PBT/vPvB assessment

Hydrocholorthiazide is slowly degraded and has low potential for bioaccumulation based on the screening criteria for B and can therefore not be considered a potential PBT substance.

References

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
- NOTOX Project 490915. Fresh water algal growth inhibition test with HCTZ DS. Final report: 09 October 2009.
- Ciba-Geigy Test No: 948032. Report on the acute toxicity test of PBS 000397.1 on Daphnia. Final report: 27 January 1995.
- NOTOX Project 485927. *Daphnia magna,* reproduction test with HCTZ DS (semi-static). Final report: 09 November 2007.
- Ciba-Geigy Test No: 811678. Full report / full reference not available.
- NOTOX Project 485928. Fish early-life stage toxicity test with HCTZ DS (semi-static). Final report: 09 November 2008.
- Ciba-Geigy Test No. 948033. Report on the test for activated sludge respiration inhibition of PBS 000397.1. Final report: 21 October 1994.
- Report No BR0137/B. [^{14}C] hydrochlorothiazide: Determination of the effects in a water-sediment system on the emergence of *Chironomus riparius* using spiked sediment. Final report: 03 March 2010.
- Report No BR0030/B. [^{14}C]Hydrochlorothiazide: 28 day ready biodegradation. 06 October 2009.
- Report No BR0040/B. HYDROCHLOROTHIAZIDE: Aerobic Transformation in Aquatic Sediment Systems. Final report: 02 February 2010.
- NOTOX Project 490916. Determination of the partition coefficient (n-octanol/water) of HCTZ DS. Final report: 01 July 2009.

- ESIDREX® (hydrochlorothiazide) Core Data Sheet Version 2.0. September 2014.

Valsartan

Miljörisk: Användning av valsartan har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Valsartan bryts ned i miljön.
Bioackumulering: Valsartan har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^9*(100-R))/(365*P*V*D*100) = 1.5*10^{-6} * 1395.7 * 100$

PEC = 0.209 µg/L

Where:

A = 1395.7 kg (total sold amount API in Sweden year 2015, data from IMS Health).

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 = $9 *10^6$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green algae (Pseudokirchneriella subspicata) (OECD201) (NOTOX Project 490976):
EC50 72 h (growth rate) > 100.0 mg/L
NOEC = 100.0 mg/L

Crustacean (Daphnia magna):
Acute toxicity
EC50 48 h (immobilisation) > 100.0 mg/L (OECD202) (ECOTOXICOLOGY CIGY NO. 948128)
Chronic toxicity
NOEC 21 days (parental mortality and reproduction) = 5.6 mg/L (OECD 211) (NOTOX Study No. 464434)

Fish:
Acute toxicity (*Oncorhynchus mykiss*, rainbow trout)
LC50 96 h (mortality) > 100.0 mg/L (OECD203) (ECOTOXICOLOGY CIGY NO. 948130)
Chronic toxicity (*Pimephales promelas,* fathead minnow)
NOEC 30 days = 10.0 mg/L; no effect up to the highest concentration tested (OECD 210) (NOTOX Study No. 464445)

Other ecotoxicity data:
Bacterial respiration inhibition
EC_{50} 3 h > 750 mg/L
NOEC = 750 mg/L (activated sludge respiration inhibition) (OECD209) (NOTOX Project 490977)

PNEC derivation:
PNEC = 560 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for *Daphnia magna* reproduction has been used for this calculation.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.209 µg/L / 560 µg/L = 0.00037, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of valsartan has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:

0 % degradation in 28 days, not readily biodegradable (92/69/EC (L383) C.4-C). (ECOTOXICOLOGY CIGY NO. 948127)

Simulation studies:

DT_{50} (total system) = 12.0 – 16.1 days

DT_{90} (total system) = 39.8 – 53.6 days (OECD 308, 191 days). (RCC Study No. B40590)

< 15 % parent substance remaining at the end of the study

45-50 % non-extractable residues at the end of the study (up to two times: acetonitrile:water (4:1, v/v), followed by soxhlet acetonitrile: water (4:1, v/v))

Justification of chosen degradation phrase:

According to the pass criteria for OECD308 studies, valsartan can be classified as 'Valsartan is degraded in the environment' (DT_{50} for total system < 32 days)

Bioaccumulation

Partitioning coefficient:

Log Dow = 1.2 at pH 7 (OECD117)

Log P = 2.8 at pH 2.5 (NOTOX Project 490979)

Justification of chosen bioaccumulation phrase:

Since log Dow < 4 at pH 7, valsartan has low potential for bioaccumulation.

Excretion (metabolism)

Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. (Diovan® (valsartan) Core Data Sheet, 2014)

PBT/vPvB assessment

Valsartan cannot be considered a potential PBT substance.

References

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
- NOTOX Project 490976. Fresh water algal growth inhibition test with valsartan/DS 21. Final report: August 04, 2009.
- ECOTOXICOLOGY CIGY NO.948128.
- NOTOX Study No. 464434. *Daphnia magna* reproduction test with VAA489 VAL (semi-static). Final Report: Sept 26, 2006.
- ECOTOXICOLOGY CIGY NO. 948130.

- NOTOX Study No. 464445. Fish early-life stage toxicity test with VAA489 VAL (semi-static). Final Report: July 12, 2006.
- NOTOX Project 490977. Activated sludge respiration inhibition test with valsartan/DS 21. Final report: August 20, 2009.
- ECOTOXICOLOGY CIGY NO. 948127.
- RCC Study No. B40590.
- NOTOX Project 490979. Determination of the partition coefficient of valsartan/DS 21. Final report: July 01, 2009.
- DIOVAN® (valsartan). Core Data Sheet. Version 2.0. 03-Dec-2014.