FASS

Afinitor®

Novartis

Tablett 5 mg

(vita till gulaktiga, avlånga tabletter med cirka 12,1 mm i längd och 4,9 mm i bredd, med fasade kanter och utan skåra, präglade med "5" på ena sidan och "NVR" på den andra)

Antineoplastiska medel, övriga antineoplastiska medel, proteinkinashämmare

Aktiv substans:

Everolimus

ATC-kod:

L01EG02

Läkemedel från Novartis omfattas av Läkemedelsförsäkringen. Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Everolimus

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

Nedbrytning: Everolimus bryts ned i miljön.
Bioackumulering: Everolimus har låg potential att bioackumuleras.

Detaljerad miljöinformation

Detailed background information

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 = 0.000131 µg/L = 0.131 ng/L

Where:
A = 0.9555 kg (total sold amount API in Sweden year 2021, data from IQVIA).
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) (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 subcapitata) (OECD 201) (Harlan Laboratories Study D53915)*:*

EC_{10} 72 h (growth rate) = 1.9 µg/L

NOEC 72 h (growth rate) = 1.5 µg/L

*Crustacean (*Waterflea, *Daphnia magna):*

Acute toxicity

EC50 48 h (immobilisation) > 8.0 mg/L, maximum testing concentration due to the substance's water solubility limit (92/69/EC (L383) C.2) (NOTOX Study No. 246768)

Chronic toxicity

NOEC 21 days (growth, body length) = 0.014 µg/L (OECD 211) (Harlan Laboratories Study C65478)

*Fish (*Zebrafish, *Danio rerio):*

Acute toxicity

LC50 96 h (lethality) > 18.4 mg/L, maximum testing concentration due to the substance's water solubility limit (92/69/EEC (L383) C1) (NOTOX Study No. 306113)

Chronic toxicity

NOEC 35 days (survival of larvae and juvenile fish, body length, body wet weight) = 2.1 µg/L (OECD 210) (Harlan Laboratories Study C65467)

Other ecotoxicity data:

Bacterial respiration inhibition (activated sludge microorganisms)

EC_{20} 3 h > 1000.0 mg/L (87/302/EEC, Part C), (Ecotox Test No. G550 05)

Sediment-dwelling organisms (Chironomus riparius, non-biting midge)

NOEC 28 days (development rate of female midges) = 2.5 mg/kg (OECD 218) (Harlan Laboratories Study D45714)

PNEC = 0.014 µg/L / 10 = 0.0014 µg/L = 1.4 ng/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used, if chronic toxicity values for 3 trophic levels are available. NOEC from *Daphnia magna* reproduction study (OECD 211) 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 = 0.131 ng/L / 1.4 ng/L = 0.0935, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of everolimus has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:

2.0 % degradation in 28 days, not readily biodegradable (92/69/EC (L383) C.4-D). (Ecotox Test No. G 550 06)

Transformation in water-sediment systems:

DT50 in total system = 2.0 – 3.1 days (OECD 308). (Harlan Laboratories Study C67572)

Study duration: 103 days; <15% of parent in both total systems at the end of the study

Bound residues are considered as not bioavailable (sediment extraction: 4x with acetonitrile/water 4:1, 1x Soxhlet extraction using acetonitrile/water (4:1; v/v))

Justification of chosen degradation phrase:

According to the classification scheme proposed for the OECD308 studies in the update of the 'Environmental classification of pharmaceuticals at www.fass.se - Guidance for pharmaceutical companies' of 2012, everolimus can be classified as ‘Everolimus is degraded in the environment'.

Bioaccumulation

Bioconcentration factor (BCF):

Steady state BCF = 23 (plateau level at 10-14 days) (OECD 305). (Harlan Study Number D58696)

Partitioning coefficient:

Log Kow = 4.0 (92/69/EC (L383) A.8). (NOTOX Study No. 255667)

Justification of chosen bioaccumulation phrase:

Since BCF < 500, everolimus has low potential for bioaccumulation.

Excretion (metabolism)

Everolimus is extensively metabolised and elimination is essentially in the form of everolimus metabolites in the bile. Elimination half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. After a single dose of [^{14}C]everolimus in renal transplant patients, the majority (80%) of radioactivity was recovered in the faeces, only a minor amount (5%) was excreted in the urine over the 10-day collection period. Parent drug was not detected in urine and faeces. (Novartis Core Data Sheet for AFINITOR (everolimus), Version 2.7, 17 June 2016)

PBT/vPvB assessment

Everolimus does not fulfil the criteria for persistence and bioaccumulation potential and can therefore not be regarded as a potential PBT or vPvB substance.

References

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

- Harlan Laboratories Study D53915. Everolimus BHT/DS 01. Toxicity to *Pseudokirchneriella subcapitata* in a 72-hour algal growth inhibition test. Final Report: 17 August 2012.
- NOTOX Study No. 246768. Acute toxicity study in Daphnia magna with RAD001 (static). Final report: 26. March 1999.
- Harlan Laboratories Study C65478. Effect of Everolimus BHT/DS 01 on survival, growth and reproduction of *Daphnia magna* in a semi-static test over three weeks. Final report: 18 January 2011.
- NOTOX Study No. 306113. 96-hour acute toxicity study in carp with RAD001 (static). Final report: 05. December 2000.
- Harlan Laboratories Study C65467 Everolimus BHT/DS 01: Toxic effects to zebra fish (*Brachydanio rerio*) in an early-life stage toxicity test. Final report: 28 February 2011.
- Ecotox Test No. G 550 05. Bacteria toxicity of RAD N BHT (Activated sludge respiration inhibition test). Final Report: 20 October 1998.
- Harlan Laboratories Study D45714. Everolimus BHT/DS 01: Effects on the development of sediment-dwelling larvae of *Chironomus riparius* in water-sediment systems with spiked sediment. Final Report: 18 June 2012.
- Ecotox Test No. G 550 06. Ready biodegradability of RAD001 N BHT (Manometric respirometry test). Final Report: 16 October 1998.
- Harlan Laboratories Study C67572. [^{14}C]Everolimus BHT/DS 01: route and rate of degradation in aerobic aquatic sediment systems. Final Report: 17 February 2012.
- Harlan Study Number D58696. [^{14}C]Everolimus: Bioconcentration flow-through test in the rainbow trout (*Oncorhynchus mykiss*). Final Report: 07 March 2013.

- NOTOX Study No. 255667. Determination of the partition coefficient (n-octanol/water) of RAD001. Final Report: 14 July 1999.
- Novartis Core Data Sheet for AFINITOR (everolimus), Version 2.7, 17 June 2016