FASS

Signifor®

Recordati

Injektionsvätska, lösning 0,6 mg
(Klar, färglös lösning)

Hypofys- och hypotalamushormoner samt analoger, somatostatinanaloger

Aktiv substans:
Pasireotid

ATC-kod:
H01CB05

Läkemedel från Recordati omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Pasireotid

Miljörisk: Användning av pasireotid har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Pasireotid bryts ned i miljön.
Bioackumulering: Pasireotid 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) = $(A*10^9*(100-R))/(365*P*V*D*100) = 1.37 * 10^{-6} * A * (100-R) = 8.08* 10^{-7}$ µg/L

Where:

A = 0.0059 kg (0.0056 kg pasireotide embonate and 0.0003 kg pasireotide) (total sold amount API in Sweden year 2021, data from IQVIA).

R = 0 % removal rate.

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 (Selenastrum capricornutum) (92/69/EC (L383) C.3) (ARC Study No.: NOV157)*:*

EC50 72 h (biomass) = 91.0 µg/L

NOEC 72 h = 50.0 µg/L

Crustacean (Daphnia magna, waterflea*):*

Acute toxicity

EC50 48 h (immobilisation) = 100.0 mg/L (OECD202) (ARC Study No.: NOV158)

Fish:

Acute toxicity (*Danio rerio,* zebra fish)
LC50 96 h (mortality) > 100.0 mg/L (OECD203) (ARC Study No.: NOV159)
Chronic toxicity (*Danio rerio,* zebrafish)
NOEC 35 days (fish weight) = 3800 µg/L (OECD 210) ((Harlan Study No. D55491)

Amphibians (*Xenopus laevis*, African clawed frog):
Chronic toxicity:
NOEC 21 days ≥ 3600 µg/L (highest concentration tested) (OECD231) (Harlan Study No. D55502)

Other ecotoxicity data:
Bacterial respiration inhibition
EC_{50} 3 h = 221.0 mg/L (activated sludge respiration inhibition) (OECD209) (ARC Study No.: NOV160)

PNEC derivation:
PNEC = 1.0 µg/L
PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor used, based on the fact that three chronic toxicity studies were available, but only covering two trophic levels. The most sensitive species in acute as well as chronic studies was algae. The NOEC for algae growth inhibition was therefore used for PNEC derivation.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = $8.08 * 10^{-7}$ µg/L / 1.0 µg/L = 0.000000808, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of pasireotide has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:

14.8 % degradation in 28 days, not readily biodegradable (92/69/EC (L383) C.4-B). (ARC Study No.: NOV161)

Simulation studies:

DT_{50} (total system) = 0.18 – 0.32 days (OECD 308). (Harlan Study No. D55524)

After application of pasireotide to the water/sediment systems, the radioactivity decreased to < 1% of applied radioactivity (AR) by day 56 in both systems. In the sediment, the extractable radioactivity increased from 0.3 and 0.4% at time 0 to 15 and 20% on day 14 and decreased to 12% by day 56 and 11% by day 99, in the two different systems, respectively. The non-extractable radioactivity increased from 11% at time 0 to 77% and 83% on day 7 and decreased to 73% and 74% by day 99. Radioactive CO2 increased to 9.1 and 10% by day 99 while organic volatiles reached at most 0.1% in both systems. In the water phases of the two systems the parent decreased to 1.4% and 0.9 % by day 14. In the sediment extracts, the parent appeared on day 2 at 3.0% and 2.3% and declined to 1.6% by day 14 in one of the two systems and to 11% on day 2 and to levels below 4% thereafter in the second system. No metabolites, which accounted for ≥ 10% were found. Sediment was extracted in acetonitrile/water 80/20 (v/v) at room temperature (ambient extraction) for 30 min at 250 rpm and then under reflux in 0.1 N HCl/acetonitrile (50/50; v/v) for 4 hours.

Justification of chosen degradation phrase:

Pasireotide is not readily biodegradable. However, a study on transformation in water/sediment systems following OECD testing guideline 308, showed DT50 values in the total system, which are significantly below the pass criteria of DT50 ≤ 32 days. The phrase “Pasireotide is degraded in the environment” is thus chosen.

Bioaccumulation

Partitioning coefficient:

Log P = -2.1 without pH adjustment (92/69/EC (L383) A.8). (ARC Study Nr. NOV156 D)

Justification of chosen bioaccumulation phrase:

Since log P < 4, pasireotide has low potential for bioaccumulation.

Excretion (metabolism)

Pasireotide s.c. is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route. In a human ADME study with pasireotide s.c. administered as with a single dose of 600 microgram 55.9 ± 6.63% of the radioactivity dose was recovered over the first 10 days post dosing, including 48.3 ± 8.16% of the radioactivity in feces and 7.63 ± 2.03% in urine. (Novartis Core Data Sheet Signifor® (pasireotide)).

PBT/vPvB assessment

Pasireotide does not fulfil the criteria for a PBT substance, as it is neither persistent, nor bioaccumulative nor toxic according to the EU criteria for PBT.

References

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

ARC Study No.: NOV157. SOM230 BTA: Algae (*Selenastrum capricornutum*) growth inhibition test. Final report: January 25, 2005.

ARC Study No.: NOV158. SOM230 BTA: Acute toxicity study for *Daphnia magna*. Final report: February 07, 2005.

ARC Study No.: NOV159. SOM230 BTA: Acute toxicity study for fish. Final report: February 07, 2005.

Harlan Study No. D55491. SOM230-BTA: Toxic effects to zebra fish (*Danio rerio*) in an early-life stage toxicity test. Final report: September 23, 2013.

Harlan Study No. D55502. SOM230-BTA: Effects to larvae of *Xenopus laevis* in an amphibian metamorphosis assay. Final report: September 23, 2013.

ARC Study No.: NOV161. SOM230 BTA: Ready biodegradability, modified OECD Screening Test. Final report: September 30, 2004.

Harlan Study No. D55524. SOM230-BTA: Route and rate of degradation of [^{14}C]SOM230-BTA in aerobic aquatic sediment systems. Final report: September 20, 2013.

ARC Study Nr. NOV156 D. SOM230 BTA: Partition coefficient n-octanol/water. Final report: December 21, 2004.

Novartis Core Data Sheet SIGNIFOR® (pasireotide), Version 3.1, 23 December 2016.