FASS

Loratadin Orifarm

M (℞) Ff

Orifarm Generics AB

Tablett 10 mg

(Vit, rund, platt med skåra)

Antihistamin

Aktiv substans:

Loratadin

ATC-kod:

R06AX13

Läkemedel från Orifarm Generics AB omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för loratadin är framtagen av företaget Bayer för Clarityn®

Miljörisk: Användning av loratadin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Loratadin är potentiellt persistent.
Bioackumulering: Loratadin 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) = 0.0886 µg/L

Where:

A = 996.51 kg (total sold amount API in Sweden year 2023, data from IQVIA / LIF)

R = 35.11 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)

P = number of inhabitants in Sweden = 10 *10^6

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

D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Reference I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Algae (*green algae*, Raphidocelis subcapitata):*

NOEC 72 hours (growth rate) = 53 µg/L, EC_{50} 72 hours (growth rate) = >950 µg/L. Guideline OECD 201. (Reference II)

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

Acute toxicity

EC_{50} 48 hours (immobilization) = 3100 µg/L. Guideline FDA TAD 4.08. (Reference III)

EC_{50} 48 hours (immobilization) = 830 µg/L. Guideline OECD 202. (Reference IV)

Chronic toxicity

NOEC 21 days (reproduction) = 78 µg/L. Guideline OECD 211. (Reference V)

*Fish (*Bluegill sunfish, *Lepomis macrochirus)*

Acute toxicity

LC_{50} 96 hours (mortality) = 820 µg/L. Guideline FDA TAD 4.11. (Reference VI)

LC_{50} 96 hours (mortality) = 382 µg/L. Guideline OECD 203. (Reference VII)

Fish (Rainbow trout, *Oncorhynchus mykiss)*

Acute toxicity

LC_{50} 96 hours (mortality) = 325 µg/L. Guideline OECD 203. (Reference VIII)

Fish (Fathead minnow, *Pimephales promelas*)

Chronic toxicity

NOEC 28 days (hatching success, survival, growth, length, dry weight) = 84 µg/L. Guideline OECD 210. (Reference IX)

Sediment dwelling organism (Midge larvae, *Chironomus riparius)*

NOEC 28 days (emergence, development rate) = 80 mg/kg. Guideline OECD 218. (Reference X)

Activated sludge microorganisms

NOEC 3 hours (respiration inhibition) = >1000 mg/L. Guideline OECD 209. (Reference XI)

The PNEC was calculated by division of the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group were algae and the lowest effect level was reported as NOEC = 53 µg/L. The regulatory default standard AF of 10 was used, which is applicable when there are chronic aquatic toxicity studies representing the three trophic levels (algae, crustaceans, and fish).

PNEC = 53 µg/L / 10 = 5.3 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.0886 µg/L / 5.3 µg/L = 0.02.

Justification of chosen environmental risk phrase:

A risk quotient of ≤ 0.1 qualifies for the phrase “Use of loratadine has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:

In a study on the aerobic biodegradability in water a mixed microbial inoculum from soil and sewage treatment plant secondary effluent was exposed to ^{14}C-loratadine at 0.102 mg/L in the dark at 22 ± 3ºC for 28 days. Prior to the test the microbial inoculum was adapted to loratadine for a period of 13 days. The test substance, reference substance (^{14}C-glucose) and blank control were tested in triplicate. Evolved $^{14}CO_2$ was measured at sixteen timepoints during the exposure period. The study reported 0.1% biodegradation in 28 days, loratadine was not readily biodegradable. Guideline FDA TAD 3.11. (Reference XII)

Simulation studies:

A simulation test to assess the aerobic biodegradability in activated sludge according to OECD 314B was performed using ^{14}C-loratadine. Single replicate test vessels per timepoint were prepared for the biotic, abiotic and positive control treatments and maintained in the dark at 20 ± 2ºC for 28 days. 500 mL of sludge inoculum obtained from a wastewater treatment plant dealing primarily with domestic sewage was used (the inoculum for the abiotic treatment was sterilised prior to use). The biotic and abiotic

test vessels were dosed with ^{14}C-loratadine at approximately 0.50 mg/L. The positive control was dosed with ^{14}C-sodium benzoate at approximately 1.0 mg/L. A flow-through system with trapping solutions was used during the incubation to capture any evolved $^{14}CO_2$ and/or volatiles. Samples were analysed at 0, 1, 3, 7, 14, 21 and 28 days after application. Sludge test solutions and trapping solutions were analysed directly by liquid scintillation counting (LSC). Sludge extracts were analysed by liquid scintillation counting (LSC) and high performance liquid chromatography with radiochemical detection (radio-HPLC) to determine the amount of ^{14}C-loratadine and quantify any transformation products.
The mass balance was >90.4% applied radioactivity (% AR) throughout the exposure period. In both the biotic and abiotic systems there was minimal evolution of $^{14}CO_2$ and/or volatiles throughout the incubation period (≤0.4% AR). There was no observable primary degradation of ^{14}C-loratadine in the abiotic system, while in the biotic system there was evidence with ^{14}C-loratadine concentrations declining steadily to 38% AR after 28 days. Two additional regions of radioactivity were detected with the first peaking at 8.4% AR on day 14 and the second peaking at 38.7% AR on day 21. This study reported a primary degradation half-life for loratadine DT_{50} = 20.32 days and an overall elimination rate constant k_e of 0.0341 days^{-1}. Guideline OECD 314B.
(Reference XIII)
A further test was conducted considering the degradation of ^{14}C-loratadine in water-sediment systems according to OECD 308. ^{14}C-loratadine was applied to the water phase of two sediment/water systems with differing properties at approximately 0.5 mg/L and

incubated in the dark at 20 ± 2ºC for 102 days. Duplicate samples were analysed at 0, 3, 14, 28, 56 and 102 days after application. A flow-through system with trapping solutions was used during the incubation to capture any evolved $^{14}CO_2$ and/or volatiles. The water and sediment extracts were analysed by LSC and radio-HPLC to determine the amount of ^{14}C-loratadine and quantify any transformation products. Sediment-bound residues were determined by oxidative combustion followed by LSC while trapping solutions were analysed directly by LSC.
The mass balance was >91.3% AR throughout the exposure period. After 14 days the majority of radioactivity was associated with the sediment phase and at the end of incubation bound residues were at 16.3 - 20.2% AR. There was minimal evolution of $^{14}CO_2$ and volatiles throughout the incubation period (<1% AR).

Concentrations of ^{14}C-loratadine declined slowly in the water-sediment systems with evidence of transformation products formation but combined they represented less than 10% AR. This study reported a half-life of loratadine in water DT_{50} = 13 - 20 days and in the total system DT_{50} = 217 – 301 days. Guideline OECD 308. (Reference XIV)

Abiotic degradation

Hydrolysis:

This study reported the substance was hydrolytically stable. Guideline FDA TAD 3.09. (Reference XV)

Photolysis:

This study reported a DT_{50} = 8.2 - 13.6 days. Guideline FDA TAD 3.10. (Reference XVI)

SimpleTreat modelling – elimination in sewage treatment plants

The SimpleTreat model (v4.1) was used to estimate the fraction of loratadine that is retained in sewage treatment plant and does not enter the surface water compartment. The calculation was based on experimental physico-chemical data of loratadine. Molecular weight: 382.9 g/mol, octanol-water partition coefficient (K_{OW}): 213.8 at pH 7, vapour pressure: <1.17 x 10^{-4} Pa at 24°C, water solubility: 1.45 mg/L at pH 7 and 25°C, sludge organic carbon partition coefficient (K_{OC}): 3911 and biodegradation: none.

(Reference XVII to XXI)

Justification if R does not equal 0, modelling results using SimpleTreat:

SimpleTreat calculated the release to surface water after sewage treatment as 64.89%, i.e., 35.11% was eliminated due to by sorption to sludge while there was no emission to air. The PEC calculation was refined taking account of this elimination.

Justification of chosen degradation phrase:

Loratadine is hydrolytically stable, not readily biodegradable with a whole water/sediment system DT_{50} > 120 days, which qualifies for the phrase “Loratadine is potentially persistent.”

Bioaccumulation

Partitioning coefficient:

The octanol/water partition coefficient (Kow) was established using ^{14}C-loratadine and the shake-flask method at 25^{o}C. Octanol and water concentrations were measured by LSC and Kow was determined at two concentrations and three pH levels (5, 7 and 9). The log D_{ow} was reported as 2.33 at pH 7. Guideline FDA TAD 3.02.

(Reference XVII)

Justification of chosen bioaccumulation phrase:

As the log D_{ow} was < 4 loratadine is not considered bioaccumulative which qualifies for the phrase “Loratadine has low potential for bioaccumulation.”

Excretion (metabolism)

Loratadine is metabolized to the active molecule desloratadine, excretion occurs mainly in the metabolized form (conjugated).

References

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