FASS

Maxalt®

Organon Sweden

Tablett 5 mg

(ljusrosa, kapselformade, märkta MSD på ena sidan och 266 på den andra)

Medel mot migrän

Aktiv substans:

Rizatriptan

ATC-kod:

N02CC04

Läkemedel från Organon Sweden omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Rizatriptan

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

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$PEC\ (\mu g/l) = (A*10^{9}*(100-R))/(365*P*V*D*100) = 1{,}5*10^{-6}*A(100-R)$

PEC = 0.0007 µg/l

Where:
A = 4.7 kg (total sold amount API in Sweden year 2020, data from IQVIA) (Ref I)
R = 0% removal rate (worst case assumption)

P = number of inhabitants in Sweden = $9 * 10^6$
V (l/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. II)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. II)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green algae (*Pseudokirchneriella subcapitata*) (OECD 201) (Ref. III):
EC_{50} 72 h (growth rate and yield) > 100 mg/l
NOEC 72 h (growth rate and yield) = 48 mg/l

Crustacean, water flea (*Daphnia magna*) (OECD 211) (Ref. IV):
Chronic toxicity
NOEC 21 d (survival and reproduction) = 110 mg/l; no effects seen at highest concentration tested

Fish, fathead minnow (*Pimephales promelas*) (OECD 210) (Ref. V):
Chronic toxicity
NOEC 32 d (reproduction and growth) = 9.6 mg/l; no effects seen at highest concentration tested

PNEC = 960 µg/l (9600 µg/l / 10 based on the most sensitive chronic NOEC for the fathead minnow and an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.0014/960 = 1.4×10^{-6}, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of rizatriptan has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Degradability (OECD 308) (Ref. VI)

The biodegradation of [^{14}C]rizatriptan was studied at a concentration of 1.0 mg/l and a temperature of 20 ± 2 °C for 99 days in two aerobic sediments varying in pH, textural characteristics, organic matter content and microbial content with associated overlying waters. Water/sediment samples from each system were analyzed at 0, 1, 5, 14, 28, 56 and 99 days after dosing.

The untreated flooded sediment samples were equilibrated under aerobic conditions for at least one week. Following equilibration, the water layers of each of the systems were treated with [^{14}C]rizatriptan to achieve a final nominal concentration of approximately 1.0 mg/L in the water layer. The aerobic incubation of treated test systems was performed by drawing hydrated air through the headspace of the test vessels for 99 days. Potassium hydroxide (KOH) and ethylene glycol organic volatiles traps were used in flow through aerobic test systems to collect $^{14}CO_2$ and any volatile components that evolved during the study.

At each sampling interval, the sediment samples from each test system were separated into water and sediment fractions. The sediment was then extracted once with acetonitrile:purified reagent water:trifluoroacetic acid (80:20:0.1, v:v:v), once with acetonitrile:purified reagent water:trifuoroacetic acid (80:20:0.5, v:v:v) and once with acetonitrile:purified reagent water:trifluoroacetic acid (80:20:1.0, v:v:v) for a total of three extractions. The third extraction was not conducted on the Day 0 sediment samples since less than 2% of applied radioactivity (% AR) was recovered from the first two extractions. The water and sediment extracts were radioassayed by LSC and then analyzed by high performance liquid

chromatography with radiochemical detection (HPLC/RAM) to quantify [^{14}C]rizatriptan and degradation products in the fractions. Radioactivity in the post extracted solids (sediment bound) was quantified by combustion analysis and the liquid volatile organic traps were radioassayed by LSC.

Results were as follows:

Table 1: Average recovery for the water layer, sediment extractable, bound residues, volatile gases and total test systems at Day 99

PARAMETER	MATERIAL BALANCE, % APPLIED RADIOACTIVITY (AR) AT DAY 99
Water Layer	
Taunton River aerobic test systems	4,1%
Weweantic River aerobic test systems	3,2%
Sediment Extractable	
Taunton River aerobic test systems	24,2%
Weweantic River aerobic test systems	26,8%
Sediment Bound Residues	
Taunton River aerobic test systems	49,2%
Weweantic River aerobic test systems	45,5%
Volatile Gases (% $^{14}CO_2$ + % VOC)	
Taunton River aerobic test systems	18,2%
Weweantic River aerobic test systems	18,5%
Total	
Taunton River aerobic test systems	95,6%
Weweantic River aerobic test systems	94,1%
Average Recovery[a]	**Day 0 through 99**
Taunton River aerobic test systems	98,7%
Weweantic River aerobic test systems	97,3%

[a] Average recovery calculated from Day 0, 1, 5, 14, 29, 56 and 99

Table 2: Elimination rate of [14C]rizatriptan

ELIMINATION RATE	OBSERVED DT_{50} (DAYS)
Water Layer	
Taunton River aerobic test systems	3.0
Weweantic River aerobic test systems	1.9
Total water/sediment	
Taunton River aerobic test systems	8.6
Weweantic River aerobic test systems	5.9

Evidence of primary biodegradation was observed for [^{14}C]rizatriptan in the aerobic water/sediment test samples. One major region of radioactivity (≥10% AR) was observed at retention time of 8.0 minutes (Met 1) in the sediment extractable phase for both the Taunton and Weweantic River systems. Several minor regions of radioactivity were observed at 8.9 minutes and 9.4 minutes in some of the chromatograms for

the Taunton River and Weweantic River test samples. In all cases, these minor peaks represented less than 10% AR in water and sediment extracts and were not considered further.

[^{14}C]Met 1 was isolated from [^{14}C]rizatriptan soil metabolism sample using HPLC and then identified using HPLC coupled with radio-detector and MS/MS. Positive and negative Q1MS full scan and negative product ion scan modes were used to generate and differentiate fragments. The proposed structure for unknown [^{14}C]Met 1 was 2-(5-(1H-1,2,4-triazol-1-yl)methyl-1H-indol-3-yl)ethanol. Average material balance ranged from 94.1 to 100.5% AR over the course of the 99-day study.

Ultimate biodegradation was observed in the aerobic test systems. The cumulative amount of evolved $^{14}CO_2$ was 18.2% AR for the Taunton River and 18.5% AR for the Weweantic River aerobic test systems at Day 99. Negligible radioactivity (≤0.1% AR) was detected as volatile organic in the aerobic test systems accumulatively at Day 99. The half-life of [^{14}C]rizatriptan (calculated from linear regression) in the water ranged from 1.9 to 3.0 days for the aerobic test systems. The half-life of [^{14}C]rizatriptan in the total water/sediment test systems ranged from 5.9 to 8.6 days for the aerobic test systems. The DT_{50} values for [^{14}C]rizatriptan were also estimated using CAKE software (non-linear Single First-order kinetics). Based on the kinetics evaluation, the DT_{50} values ranged from 6.2 to 8.7 days for the aerobic test systems.

Justification of chosen degradation phrase:
The DT_{50} for the total system was <32 d but there is in total >15% parent compound remaining at the end of the study (water + sediment extract); therefore the phrase “The substance is slowly degraded in the environment” is chosen.

Bioaccumulation

Partitioning coefficient (OECD 107) (Ref.VII):
Log K_{ow} = -0.649 at pH 7 (measured)

Justification of chosen bioaccumulation phrase:
Since log K_{ow} < 4 the substance has low potential for bioaccumulation.

References

I. Data from IQVIA ”Consumption assessment in kg for input to environmental classification - updated 2021 (data 2020)”.
II. 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
III. Smithers Viscient, 2012. "Rizatriptan – 72-Hour Acute Toxicity Test with Freshwater Green Alga, Pseudokirchneriella subcapitata, Following OECD Guideline 201," Study No. 359.6510, SV, Wareham, MA, USA, 02 February 2012.
IV. Smithers Viscient, 2012. "Rizatriptan – Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static-Renewal Conditions, Following OECD Guideline #211," Study No. 359.6507, SV, Wareham, MA, USA, 29 March 2012.
V. Smithers Viscient, 2013. "Rizatriptan – Early Life-Stage Toxicity Test with Fathead Minnow, Pimephales promelas, Following OECD Guideline #210," Study No. 359.6508, SV, Wareham, MA, USA, 14 January 2013.
VI. Smithers Viscient, 2012. "[14C]Rizatriptan – Aerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308," Study No. 359.6506, SV, Wareham, MA, USA, 15 November 2012.

VII. Smithers Viscient, 2012. "Rizatriptan - Determining the Partitioning Coefficient (n-Octanol/Water) by the Shake Flask Method Following OECD Guideline 107," Study No. 359.6504, SV, Wareham, MA, USA, 13 March 2012.