FASS

Sitagliptin Reddy

M

Betapharm Arzneimittel

Filmdragerad tablett 25 mg

(Tillhandahålls ej) (Vita, runda filmdragerade tabletter med "411" på ena sidan och släta på den andra sidan. Diameter på ca 6 mm.)

Diabetesmedel, Dipeptidylpeptidas-4 (DPP-4)-hämmare.

Aktiv substans:

Sitagliptin

ATC-kod:

A10BH01

Läkemedel från Betapharm Arzneimittel omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för sitagliptin är framtagen av företaget MSD för Efficib®, Janumet®, Januvia®, Ristaben, Ristfor, Steglujan, Tesavel®, Velmetia®, Xelevia®

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

Nedbrytning: Sitagliptin är potentiellt persistent.
Bioackumulering: Sitagliptin 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)

PEC = 0.28 µg/L

Where:
A = 2 011.1551 kg (49.0658 kg sitagliptin, 1.5972 kg sitagliptinfumarat, 1 628.3372 kg sitagliptinfosfatmonohydrat and 332.1549 kg sitagliptinhydrokloridmonohydrat) (total sold amount API in Sweden year 2022, data from IQVIA) (Ref I)
R = 0 % removal rate (worst case assumption)
P = number of inhabitants in Sweden = $10 *10^{6}$
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) > 39 mg/L
NOEC = 2.2 mg/L

Crustacean, water flea (Daphnia magna):
Acute toxicity
EC_{50} 48 h (immobility) = 60 mg/L (OECD 202) (Ref. IV)
NOEC = 25 mg/L

Chronic toxicity
NOEC 21 day (survival, reproduction, and growth) = 9.8 mg/L (OECD 211) (Ref. V)
No effects seen up to highest concentration tested

Fish, fathead minnow (Pimephales promelas):
Acute toxicity
LC_{50} 96 h (mortality) > 100 mg/L (OECD 203) (Ref. VI)
NOEC = 100 mg/L
No effects seen up to highest concentration tested

Chronic toxicity
NOEC 33 days (percent live normal fry, total length and dry weight) = 9.2 mg/L (OECD 210) (Ref. VII)
No effects seen up to highest concentration tested

PNEC = 220 µg/L (2200 µg/L/ 10 based on the most sensitive chronic NOEC for the green algae with an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.28/220 =0.0013, i.e. PEC/PNEC ≤ .1 which justifies the phrase "Use of sitagliptin has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Inherent Biodegradation (OECD 302B) (Ref. VIII)
7% loss of parent in 28 days

Sludge Biodegradation (OECD 314) (Ref. IX):
75% elimination (loss of parent) at Day 28, 40% evolved as CO_2

DT_{50} for loss of parent = 21.1 hours

DT_{50} for CO2 production = 108 days

Sediment Transformation (OECD 308) (Ref. X):
DT_{50}: 139 – 169 days

The aerobic and anaerobic water/sediment metabolism of MK-0431 (butaneamine-14C]L-000224715-004B006) was studied in two water/sediment systems under laboratory conditions using [14C]MK-0431. The two aerobic and two anaerobic sediments varied in textural characteristics, organic matter content and microbial content (Taunton River aerobic, Taunton River anaerobic, Weweantic River aerobic and Weweantic River anaerobic sediments). The untreated flooded sediment samples (50 g dry weight sediment plus 150 mL water) were incubated under aerobic and anaerobic conditions for at least one week. Following incubation, [14C]MK-0431 was applied to the water layers of each of the systems to achieve a final nominal concentration of

approximately 1 mg/L in the water layer. A flow-through test system was used in order to determine the aerobic rate and route of degradation of [14C]MK-0431 at a temperature of 20 ± 2ºC continuously in the dark. For the aerobic test systems, the aerobic environment was maintained by continuously bubbling hydrated air through the water layer for 103 days. The anaerobic test systems were prepared in a nitrogen atmosphere and tightly sealed throughout the study to ensure anaerobic test conditions. All test systems used potassium hydroxide (KOH) and ethylene glycol organic volatile traps to collect $14CO_2$ and any volatile components that evolved during the study. Water and sediment samples from all test systems were assayed at 0, 4, 12, 26, 60 and 103 days after application of the test substance. The test conditions outlined in the study protocol were maintained throughout the study.

Duplicate samples were analyzed from the water layer and sediment extractables at each sampling interval. The sediment was extracted two times with 300 mL of acetonitrile:water:concentrated hydrochloric acid (80:20:0.5). The water layer and sediment extractables were analyzed separately by HPLC/RAM and radioassayed using LSC to determine the amount of [14C]MK-0431 (parent) and degradation products in the samples. Radioactivity in the nonextractable sediment residues (bound sediment residues) were quantified by combustion analysis and radioassay. The liquid volatile organic traps were also radioassayed.

Results of the OECD 308 study suggest that very little primary degradation of sitagliptin occurred in the aerobic and anaerobic sediment-water systems. The times of disappearance of 50 percent of the parent (DT_{50}) from the aqueous layers were 6.5 to 20.9 days and 138.6 to 266.5 days in the aerobic and anaerobic test systems,

respectively. The results of the study also indicated that sitagliptin has the potential for sorption to sediments. The mass balance results from day 103 indicated that up to 78% of the dosed radioactivity was found in the extractable sediment fraction and up to 28% was found in the bound fraction. Percent radioactivity was primarly parent molecule (~79%) with no degradates exceeding 10% total applied radioactivity at any time. Total system half-life ranged from 136 – 169 days.

Abiotic degradation

Hydrolysis:

No significant degradation (Half life = 895 days at pH 7) (OECD 111) (Ref. XI)

Photolysis:

No potential for phototransformation between 295 and 800 nm (OECD 316) (Ref. XII)

Justification of chosen degradation phrase:

Sitagliptin is slightly degradable in biological systems, however does not meet the criteria for ready degradability. In addition, the half-life in the total system exceeded 120 days, therefore the phrase “Sitagliptin is potentially persistent in the environment” was thus chosen.

Bioaccumulation

Partitioning coefficient:

Log K_{ow} = -0.03 at pH 7 (OECD 107) (Ref. XIII)

Justification of chosen bioaccumulation phrase:

Since log K_{ow} < 4 at pH 7, the substance has low potential for bioaccumulation.

References

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IV. Toxikon Corporation, 2004. "MK-0431: Acute Toxicity to the Water Flea, Daphnia magna, Under Static Conditions," Study No., 04J0005a, Jupiter, FL, USA, 08 July 2004.

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X. Springborn Smithers Laboratories, 2007. "[14C]MK-0431: Aerobic and Anaerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308," Study No., 359.6128, SSL, Wareham, MA, USA, 05 October 2007.

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