FASS

Trajenta

MRx (F)

Boehringer Ingelheim

Filmdragerad tablett 5 mg

(8 mm diameter, rund, ljusröd, filmdragerad tablett med D5 präglat på ena sidan och Boehringer Ingelheims logotyp på den andra sidan)

DPP-4-hämmare

Aktiv substans:

Linagliptin

ATC-kod:

A10BH05

Läkemedel från Boehringer Ingelheim omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Linagliptin

Miljörisk: Användning av linagliptin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Linagliptin bryts ned långsamt i miljön.
Bioackumulering: Linagliptin 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) = $(A*10^{9}*(100-R))/ (365*P*V*D*100) = 1.37*10^{-6}*A *(100-R) = 0,00538$µg/L

Where:
A = 39,28 kg (total sold amount API in Sweden 2022, 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) (I)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (I)

Predicted No Effect Concentration (PNEC)

PNEC = 320 µg/L

The PNEC has been derived from the lowest NOEC (Daphnia magna, 21d) of 3.2 mg/L. An assessment factor of 10 is used based on the availability of a NOEC for algal growth inhibition in combination with chronic toxicity studies for the other two trophic levels in accordance with ECHA Guidelines (I).

Ecotoxicological studies

Algea (Green algea, *Pseudokirchneriella subcapitata*) (OECD 201, GLP) (II)
EC50 72h (growth rate) = 49 mg/L
NOEC 72h (growth rate) = 4.1 mg/L
EC50 72h (biomass) = 16 mg/L
NOEC 72h (biomass) = 4.1 mg/L

*Crustacean (*Water flea*, Daphnia magna)*
Chronic toxicity (OECD 211, GLP)(III):
NOEC 21d (parental mortality) = 3.2 mg/L
LOEC 21d (parental mortality) = 10 mg/L

Fish (Zebrafish*, Danio rerio*)
Chronic toxicity (OECD 210, GLP)(IV):
NOEC 35d = ≥ 12.0 mg/L (no effects, highest dose tested)

Other ecotoxicity data

Respiration inhibition of activated sludge (OECD 209, GLP)(V):
EC50 3h = 792 mg/L
NOEC 3h = 210 mg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0,00538/320 = 0,00002, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of Linagliptin has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:

In a 28d ready biodegradability study (OECD 301A, GLP) 0% biodegradation of Linagliptin was observed (VI). Based on these data Linagliptin is not readily biodegradable.

Inherent degradability:

No data on inherent biodegradability.

Simulation studies:

In an OECD 308 study (GLP)(VII), the following dissipation rates (DT_{50}) were determined in two aquatic freshwater systems, river and pond:

- Freshwater: 0.8 days (river) and 1.1 (pond)
- Sediment: 110 days (river) and 42.2 (pond)
- Total system: 5.2 days (river) and 1.6 (pond)

At the end of the study (day 100), 22.7% (river) and 4.4% (pond) of the applied radioactivity was remaining as parent compound in the two systems, respectively. The amount of non-extractable radioactivity in the sediment was high for both test systems with bound residues accounting for up to 50.9% (river) and 72.4% (pond) at day 100. Several minor degradation products were detected, none individually exceeding 10% of the applied radioactivity.

After removing the water phase from the test system, the sediment was submitted to up to four extraction steps using acetonitrile/water (4:1; v/v) at room temperature until less than 5% of the radioactivity applied was recovered. Extractions at room temperature were performed in a shaker at about 200-250 strokes per minute each for about 30 minutes. The radioactivity in the individual extracts was quantified by LSC (duplicate aliquots). Soxhlet extraction using acetonitrile/water (4:1; v/v) for 4 hours was additionally performed on the extracted sediments (except for day 0). This extraction method was performed if more than 10% of the applied radioactivity remained non-extractable. All extracts containing more than 2% of the radioactivity applied were combined and concentrated in a rotary evaporator at about 30 °C. The concentrated extracts were measured by LSC for recovery and submitted to HPLC and/ or TLC analysis. The amount of solvent used was in general about 1 mL/g sediment (wet weight basis). Reflux extraction with acetonitrile/0.1 M HCl (1:1; v/v) for at least four hours was conducted followed additionally by organic matter fractionation for one interval of the river and pond test system (day 100, duplicate determination). The radioactivity content in the reflux extracts was determined by LSC. The reflux extracts were analysed by HPLC. After all extractions, the residual sediments were dried, weighed, homogenised and their radiocarbon content was determined by LSC after combustion of up to 1.0 g aliquots.

The mineralisation of the test item and the formation of other organic volatiles was very low, accounting for < 1.5% or < 0.1% during the 100 days of incubation. In conclusion, Linagliptin rapidly dissipated from the water phase by adsorption to the sediment of both systems. Once in the sediment, its degradation proceeds at a very slow rate, mainly via the formation of bound residues and the formation of minor metabolites. Since Linagliptin has a DT_{50} of ≤ 32d, but > 15% remaining as parent compound at the end of the study in the river system, Linagliptin is considered to be slowly degraded in the environment.

Abiotic degradation
Hydrolysis: No significant degradation was observed at pH 7 and 9 at 25°C after 28 days. At pH of 12.8 and 2.2 a total of 4.3% and 11.3% impurities, respectively, was observed (VIII).

Photolysis: After 22 hours of artificial light irradiation (Suntest) a total of 4% impurities were observed (VIII).

Justification of chosen degradation phrase:
Linagliptin was not readily biodegradable (OECD 301A, GLP). Further, in an OECD Guideline 308 simulation study, Linagliptin was slowly degraded in the environment. In abiotic degradation studies, Linagliptin did not undergo significant degradation by hydrolysis or photolysis. Based on these combined data, Linagliptin is considered to be slowly degraded in the environment.

Bioaccumulation
Bioconcentration factor (BCF):
No data on bioconcentration in fish.

Partitioning coefficient:
The n-octanol/water partition coefficient was in an OECD Guideline 122 (GLP) study determined to -1.6 at pH 5.0, 0.1 at pH 7.0 and 1.5 at pH 9.0, respectively (IX).

Justification of chosen bioaccumulation phrase:

Based on the data from the OECD Guideline 122 study n-octanol/water partition coefficients of -1.6 to 1.5 at pH 5 to 9, Linagliptin is considered to have low potential for bioaccumulation.

Excretion (metabolism)

After both oral and intravenous administration, the majority of Linagliptin (~90%) was excreted unchanged in the urine and feces (X). Thus, the environmental risk assessment should be performed on the data of the parent compound.

PBT/vPvB assessment

Linagliptin is considered not to fulfil the criteria for PBT or vPvB.

References

I. European Chemicals Agency (ECHA), 2008. Guidance on information requirements and chemical safety assessment. Chapter R.10: Characterization of dose[concentration]-response for environment. http://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf
II. Boehringer Ingelheim GmbH internal report U08-0276-01, 2008
III. Boehringer Ingelheim GmbH internal report U09-0013-01, 2008
IV. Boehringer Ingelheim GmbH internal report U08-0289-01, 2008
V. Boehringer Ingelheim GmbH internal report U08-0277-01, 2008
VI. Boehringer Ingelheim GmbH internal report U08-0278-01, 1997
VII. Boehringer Ingelheim GmbH internal report U08-0279-01, 2008
VIII. Boehringer Ingelheim GmbH internal report U09-2355-01, 2009
IX. Boehringer Ingelheim GmbH internal report U09-1908-01, 2009
X. Boehringer Ingelheim GmbH Environmental Risk Assessment of Linagliptin, 2010 (U10-0020-01)