FASS

Jardiance

M ℞ (F)

Boehringer Ingelheim

Filmdragerad tablett 10 mg

(Rund, ljusgul, bikonvex, filmdragerad tablett med fasad kant, präglad med "S10" på ena sidan och Boehringer Ingelheims logo på den andra (tablettdiameter: 9,1 mm))

Natriumglukoskotransportör 2 (SGLT2) hämmare

Aktiv substans:
Empagliflozin

ATC-kod:
A10BK03

Läkemedel från Boehringer Ingelheim omfattas av Läkemedelsförsäkringen.
Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Empagliflozin

Miljörisk: Användning av empagliflozin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Empagliflozin bryts ned i miljön.
Bioackumulering: Empagliflozin 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) = $(A*10^{9}*(100-R))/ (365*P*V*D*100) = 1.37*10^{-6}*A (100-R) = 0.0729$ µg/L

Where:
A = 531,9 kg (data from 2022, provided by 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 = 240 µg/L

The PNEC has been derived from the lowest NOEC (Danio rerio, 35d) of 2.4 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
Algae (Green algae, *Pseudokirchneriella subcapitata)* (OECD 201, GLP) (II):
EC50 72h (growth rate) = ≥ 100 mg/L
NOEC 72h (growth rate) = ≥ 100 mg/L
EC50 72h (biomass) = ≥ 100 mg/L
NOEC 72h (biomass) = ≥ 100 mg/L

*Crustacean (*Water flea*, Daphnia magna)*
Chronic toxicity (OECD 211, GLP)(III):
NOEC 21d = ≥ 100 mg/L (no effects, highest dose tested)

Fish (Zebrafish*, Danio rerio*)
Chronic toxicity (OECD 210, GLP)(IV):
NOEC 35d (length, wet weight, dry weight) = 2.4 mg/L
LOEC 35d (length, wet weight, dry weight) = 11.6 mg/L

Other ecotoxicity data
Respiration inhibition of activated sludge (OECD 209, GLP)(V):
EC50 3h = ≥ 100 mg/L
NOEC 3h = ≥ 100 mg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.0729/240 = 0.00030, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of Empagliflozin has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation
Ready biodegrability:
In a 28d ready biodegradability study (OECD 301B, GLP) 0% biodegradation of Empagliflozin was observed (VI). Based on these data Empagliflozin is not readily biodegradable.

Inherent degradability:
No data on inherent biodegradability.

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

- Freshwater: 1.2 (river) and 1.1 (pond) days
- Sediment: 2.6 (river) and 1.9 (pond) days
- Total system: 1.3 (river) and 1.3 (pond) days

At the start of the study, 98.4% (river) and 100.2% (pond) of the applied radioactivity (AR) (pond) of the parent substance were measured in the water phases, decreasing to 1.2% (river) and 0% (pond) after 14 days of incubation. The amount of Empagliflozin in the sediment extracts increased with time to maximum values of 7.2% (river) and 8.0% AR (pond) on day 7 and decreased thereafter continuously to levels of 0.4% (river) and 0.2% AR (pond) on day 103.

After removing the water phase from the test system, the sediment was extracted at room temperature as follows:

- Acetonitrile (one to three times)
- Acetonitrile/0.1 M HCl (4:1;v:v) (one to two times, from day 14 onwards)

Extractions at room temperature were performed in a shaker at about 250 strokes per minute each for about 30 minutes as given in the Standard Operation Procedures. From day 7 onwards, the sediment was additionally extracted by Soxhlet extraction with acetonitrile for about 4 hours. The radioactivity in the individual extracts was quantified by LSC. The room temperature and Soxhlet extracts were then combined (if Soxhlet extract contained more than 2% of applied) and an aliquot was concentrated under reduced pressure at about 35 °C using a rotary evaporator. The concentrated extracts were re-dissolved in acetonitrile/water (1:4; v:v), and the samples were submitted to HPLC. Selected samples were additionally analyzed by TLC. After all the extractions, the residual sediments were dried, weighed, homogenized and their radiocarbon content was determined by LSC after combustion of aliquots of approximately

Non-extracted residues accounted for < 0.1% of the AR (river and pond) on time 0, peaked on day 57 at 50.5% (river) and 42.2% AR (pond) and decreased to levels of 47.2% (river) and 39.6% AR (pond) at day 103. More than 30 transformation products were detectable in the in total systems, whereof three (M1, M3 and M12) were significant, i.e. represented 10% of the AR or more. M1 constituted a maximum of 43.2% in river (day 7) and 40.1% in pond (day 1). M3 reached levels of 15.1% of AR in river and 15.2% in pond at day 7. M12 peaked at 3.8% in river (day 28) and 20.2% in pond (day 14). Some of the individual transformation products (M1 in river, M1 and M3 in pond system) showed significant amounts (> 10% of AR) in the sediments. The sum of parent Empagliflozin and its transformation products in sediment (based on total extractable radioactivity) peaked with 28.3% (river) and 27.3% (pond) on day 7. A significant amount of total radioactivity (> 10% of AR) was measured in the sediment extracts of both systems until day 57. The DT50 of the transformation products in the total system were:

- M1: 6.2 (river) and 7.9 (pond) days
- M3: 51.7 (river) and 36.8 (pond) days
- M12: 37.5 (pond) days

None of the detected transformation products showed continuously increasing concentration during the study. The mineralization accounted for 37.7 (river) and 34.8% AR (pond), while formation of organic volatiles was insignificant (<0.1% AR, river and pond).

In conclusion, Empagliflozin rapidly dissipates from the water phase by rapid biodegradation to multiple transformation products. Empagliflozin and its transformation products showed a significant distribution to the sediment. Since Empagliflozin has a DT_{50} of ≤ 32d and with < 15% remaining as parent compound at the end of the study in the two systems, Empagliflozin is considered to be degraded in the environment.

Abiotic degradation
Hydrolysis: No data on hydrolysis.
Photolysis: No data on photolysis.

Justification of chosen degradation phrase:
Empagliflozin was not readily biodegradable in a 28d ready biodegradability study (OECD 301B, GLP). However, in an OECD Guideline 308 simulation study, Empagliflozin rapidly dissipated from the water phase via degradation to multiple transformation products with very little remaining of the parent compound after 120 days (≤ 0.4%). Based on these combined data, Empagliflozin is considered to be 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 107 (GLP) study determined to 1.73 at pH 7.0 (IX).

Justification of chosen bioaccumulation phrase:
Based on the data from the OECD Guideline 107 study with an n-octanol/water partition coefficient of 1.73 at pH 7.0, Empagliflozin is considered to have low potential for bioaccumulation.

Excretion (metabolism)
After oral administration of Empagliflozin most of the radioactive dose was recovered in urine (54.4%) and feces (41.1%) (X). Unchanged Empagliflozin was the most abundant component in urine and feces, representing 43.5% and 82.9% of radioactivity, respectively. The most abundant metabolites in urine were two glucuronide conjugates (7.8-13.2% of dose) and in feces a tetrahydrofuran ring-opened carboxylic acid metabolite (1.9% of dose). Thus, the environmental risk assessment should be performed on the data of the parent compound.

PBT/vPvB assessment
Empagliflozin 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 U12-2202-01, 2012
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VI. Boehringer Ingelheim GmbH internal report U12-2205-01, 2011
VII. Boehringer Ingelheim GmbH internal report U12-2206-01, 2012
VIII. Boehringer Ingelheim GmbH internal report U13-1652-01, 2013
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X. Chen LZ, Jungnik A, Mao Y, Philip E, Sharp D, Unseld A, Seman L, Woerle HJ, Macha S (2014). Biotransformation and mass balance of the SGLT2 inhibitor empagliflozin in healthy volunteers. Xenobiotica (ahead of print, doi: 10.3109/00498254.2014.999141).