FASS

Synjardy

Boehringer Ingelheim

Filmdragerad tablett 12,5 mg/1000 mg
(Mörkt brunlila, ovala, bikonvexa, filmdragerade tabletter präglade med ”S12” och Boehringer Ingelheims logo på ena sidan och ”1 000” på den andra sidan. 21,1 mm x 9,7 mm.)

Diabetesmedel, Perorala diabetesmedel, kombinationer

Aktiva substanser (i bokstavsordning):
Empagliflozin
Metformin

ATC-kod:
A10BD20

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_requi

II. Boehringer Ingelheim GmbH internal report U12-2202-01, 2012
III. Boehringer Ingelheim GmbH internal report U12-2204-01, 2012
IV. Boehringer Ingelheim GmbH internal report U12-2596-01, 2012
V. Boehringer Ingelheim GmbH internal report U12-2203-01, 2012
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
IX. Boehringer Ingelheim GmbH internal report U12-2201-01, 2011
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).

Miljöinformationen för metformin är framtagen av företaget Novartis för Eucreas®, Icandra, Zomarist

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

Nedbrytning: Metformin bryts ned långsamt i miljön.
Bioackumulering: Metformin har låg potential att bioackumuleras.

Detaljerad miljöinformation

Disclaimer:

With the exception of the literature studies and the Novartis Core data sheet, all studies used in this Environmental Assessment are the property of Janssen. Novartis has been authorised by Janssen to use the study reports for the purpose of contributing to the Swedish www.fass.se database.

Detailed background information
Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}$ * 186664.64 * 100

PEC = 25.57 µg/L

Where:

A = 186664.64 kg metformin hydrochloride (total sold amount API in Sweden year 2021, data from IQVIA).

R = 0 % 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) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green algae (Pseudokirchneriella subspicata) (OECD201) (Springborn Smithers Study No. 13751.6179):
EC50 72 h (growth rate) > 99.0 mg/L
NOEC = 99.0 mg/L

Crustacean (Daphnia magna):
Acute toxicity
EC50 48 h (immobilisation) = 64.0 mg/L (EC Test Guideline 92/69/EEC C.2) (Cleuvers 2003)
EC_{50} 48 h (immobilisation) > 110 mg/L (OECD 202) (Springborn Smithers Study No. 13751.6180)
Chronic toxicity
NOEC 21 days = 100.0 mg/L (OECD 211) (Smithers Viscient AG Study #1149.001.230)

Fish:
Acute toxicity (*Danio rerio*, zebrafish)
LC50 96 h (mortality) > 110.0 mg/L; no effect up to the highest concentration tested (OECD203) (Springborn Smithers Study No.13751.6181)
Chronic toxicity (*Pimephales promelas,* fathead minnow)
NOEC 32 days = 10.3 mg/L; no effect up to the highest concentration tested (OECD 210) (Smithers Viscient AG Study # 1149.001.122)

Other ecotoxicity data:
Bacterial respiration inhibition
EC_{50} 3 h > 750 mg/L

NOEC = 1.5 mg/L (activated sludge respiration inhibition) (OECD209) (Smithers Viscient Study No. 13674.6228)
Sediment-dwelling organisms (Chironomus riparius, non-biting midge)
NOEC 28 days ≥ 100 mg/kg; no effect up to the highest concentration tested (OECD 218) (Smithers Viscient AG Study # 1149.001.173)
PNEC derivation:
PNEC = 1030 µg/L
PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for chronic toxicity in fish has been used for this calculation.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 25.57 µg/L / 1030 µg/L = 0.025, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of metformin has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:
35.5 % degradation in 28 days, not readily biodegradable (OECD 301B). (Smithers Viscient Study No. 13674.6229)

Simulation studies:
DT_{50} (total system) = 43.0 – 53.0 days (OECD 308, 101 days).
(Smithers Viscient Study No. 13674.6233)
At each sampling interval, the samples from each test system were separated into water and sediment fractions. The Day 0 and Day 3 sediment samples were extracted once with acetonitrile and once

with acetonitrile:purified reagent water (80:20, v:v). The Day 3 samples were extracted two additional times with acetonitrile:purified reagent water:concentrated hydrochloric acid (80:20:0.1, v:v:v) for a total of four extractions. The Day 14 to Day 101 samples were extracted once with acetonitrile and twice with acetonitrile:purified reagent water:concentrated hydrochloric acid (80:20:0.1, v:v:v) for a total of three extractions.
Ultimate biodegradation was observed in the aerobic test systems. The cumulative amount of evolved $^{14}CO_2$ was 18.0% of applied radioactivity (AR) and 2.2% AR for the two test systems at Day 101. Evidence of primary biodegradation was observed for [^{14}C] metformin hydrochloride in the aerobic water/sediment test samples. Several minor regions of radioactivity were observed in some of the chromatograms for both aquatic sediment systems. In all cases, these peaks represented less than 10% of the applied radioactivity and were not considered further.

Justification of chosen degradation phrase:
According to the pass criteria for OECD308 studies, metformin can be classified as ‘Metformin is slowly degraded in the environment' (DT_{50} for total system ≤ 120 days).

Bioaccumulation

Partitioning coefficient:
Log P = -2.48 (OECD107) (Smithers Viscient Study No. 13674.6227)
Justification of chosen bioaccumulation phrase:
Since log P < 4, metformin has low potential for bioaccumulation.

Excretion (metabolism)

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution. (Eucreas®, Novartis Core data sheet, 2016)

PBT/vPvB assessment

Metformin cannot be considered a potential PBT substance, as it is neither persistent, nor has potential for bioaccumulation or toxicity in aquatic organisms.

References

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/informa
- Springborn Smithers Study No. 13751.6179. Final report: 07 January 2011. Metformin Hydrochloride – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline #201 and the Official Journal of the European Communities L220/36, Method C.3
- Cleuvers, M. (2003), Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. Tox. Letts.

2003, 142,
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- Springborn Smithers Study No. 13751.6180. Final report: 11 January 2011. Metformin Hydrochloride - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L142/456, Method C.2
- Smithers Viscient AG Study #1149.001.230. Final report: 14 December 2011. Metformin HCl: Chronic reproduction test with daphnids (*Daphnia magna*) under semi-static conditions
- Springborn Smithers Study No.13751.6181. Final report: 14 January 2011. Metformin Hydrochloride - Acute Toxicity to Zebra Fish (*Brachydanio rerio*) Under Static Conditions, Following OECD Guideline Number 203 and The Official Journal of the European Communities L 142/446, Method C.1

- Smithers Viscient AG Study # 1149.001.122. Final report: 15 December 2011. Metformin HCl: Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*) under Flow-through Conditions
- Smithers Viscient Study No. 13674.6228. Final report: 06 March 2012. Metformin Hydrochloride - Activated Sludge Respiration Inhibition Test Following OECD Guideline 209
- Smithers Viscient AG Study # 1149.001.173. ^{14}C-Metformin HCl: Chronic toxicity test with midge larvae (*Chironomus riparius*) in a water/sediment system. Final report: 14 December 2011.

- Smithers Viscient Study No. 13674.6229. Final report: 03 November 2011. Metformin hydrochloride – Determination of the Biodegradability of a Test Substance Based on OECD Method 301B (CO_2 Evolution Test)
- Smithers Viscient Study No. 13674.6233. Final report: 29 December 2011. [^{14}C]Metformin Hydrochloride - Aerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308
- Smithers Viscient Study No.13674.6227. Final report: 3 November 2011. Metformin Hydrochloride - Determining the Partitioning Coefficient (n-Octanol/Water) by the Flask-Shaking Method Following OECD Guideline 107
- Eucreas® (vildagliptin metformin fixed combination), Novartis Core data sheet, Version 3.0, 28 November 2016.