

## Glyxambi

**M R (F)****Boehringer Ingelheim**

Filmdragerad tablett 10 mg/5 mg

(Ljusbula, rundat triangelformade, släta, filmdragerade tabletter med fasad kant. Ena sidan är präglad med Boehringer Ingelheims företagslogo och den andra med "10/5" (tablettstorlek: varje sida 8 mm).)

Diabetesmedel, kombinationer av perorala blodglukossänkande läkemedel

**Aktiva substanser (i bokstavsordning):**

Empagliflozin

Linagliptin

**ATC-kod:**

A10BD19

Läkemedel från Boehringer Ingelheim omfattas av Läkemedelsförsäkringen.

## 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:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A$$
$$(100 - R) = 0.0729 \mu\text{g/L}$$

Where:

A = 531,9 kg (data from 2022, provided by IQVIA).

R = 0 % removal rate.

P = number of inhabitants in Sweden =  $10 \cdot 10^6$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (l)

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

#### *Predicted No Effect Concentration (PNEC)*

$$\text{PNEC} = 240 \mu\text{g/L}$$

*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) =  $\geq 100$  mg/L

NOEC 72h (growth rate) =  $\geq 100$  mg/L

EC50 72h (biomass) =  $\geq 100$  mg/L

NOEC 72h (biomass) =  $\geq 100$  mg/L

*Crustacean* (Water flea, *Daphnia magna*)

Chronic toxicity (OECD 211, GLP)(III):

NOEC 21d =  $\geq 100$  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 =  $\geq 100$  mg/L

NOEC 3h =  $\geq 100$  mg/L

#### **Environmental risk classification (PEC/PNEC ratio)**

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

## Degradation

### *Biotic degradation*

#### *Ready biodegradability:*

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  $\leq 32$  d 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 ( $\leq 0.4\%$ ). 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](http://echa.europa.eu/documents/10162/13632/information_requi)
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- 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).

## 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:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R) = 0,00538 \mu\text{g/L}$$

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 =  $10 \cdot 10^6$

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)

$$\text{PNEC} = 320 \mu\text{g/L}$$

*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*

Algae (Green algae, *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 =  $\geq 12.0$  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.  $PEC/PNEC \leq 0.1$  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<sub>50</sub>) 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  $\leq 32$ d, 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.  
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