



Xigduo

M R F

AstraZeneca

Filmdragerad tablett 5 mg/1000 mg

(Gula, bikonvexa, 10,5 x 21,5 mm ovala, filmdragerade tabletter med "5/1000"präglat på ena sidan och "1069"präglat på andra sidan)

Diabetesmedel, Perorala blodglukossänkande medel, kombinationer

Aktiva substanser (i bokstavsordning):

Dapagliflozin

Metformin

ATC-kod:

A10BD15

Läkemedel från AstraZeneca omfattas av Läkemedelsförsäkringen.

Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Dapagliflozin

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

Nedbrytning: Dapagliflozin bryts ned långsamt i miljön.

Bioackumulering: Dapagliflozin har låg potential att bioackumuleras.

Detaljerad miljöinformation

$$\text{PEC/PNEC} = 0.0032/100 = 3.2 \times 10^{-5}$$

$$\text{PEC/PNEC} \leq 0.1$$

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is based on following data and calculated using the equation outlined in the fass.se guidance (Ref 1):

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

$$PEC (\mu\text{g/L}) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

A (kg/year) = 23.54 kg, total sold amount API in Sweden year 2020, data from IQVIA Health.

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) R = 0.

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

V (L/day) = volume of wastewater per capita and day = 200 (default, Ref 1)

D = factor for dilution of waste water by surface water flow = 10 (default, Ref 1)

(Note: The factor 10^9 converts the quantity used from kg to μg).

$$PEC = 1.37 \cdot 10^{-6} \cdot 23.54 \cdot (100 - 0) = 0.0032 \mu\text{g/L}$$

(Note: Whilst dapagliflozin is metabolised in humans, little is known about the ecotoxicity of the metabolites. Hence, as a worst case, for the purpose of this calculation, it is assumed that 100% of excreted metabolites have the same ecotoxicity as parent dapagliflozin).

Metabolism

Dapagliflozin is rapidly adsorbed and extensively metabolised. Dapagliflozin and its related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin (Ref 2). After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug (Ref 3). Therefore, the patient use of dapagliflozin is likely to result mainly in metabolites and, to a lesser extent, the active moiety entering the environment.

Ecotoxicity data

Study Type	Method	Result	Ref
Activated sludge, respiration inhibition test	OECD209	3 h EC50 >200 mg/L 3 h NOEC = 200 mg/L	4
Toxicity to green algae, <i>Pseudokirchinella subcapitata</i> , growth inhibition test	OECD201	72 hour NOEC _{growth rate} = 37 mg/L 72 hour LOEC _{growth rate} = 67 mg/L 72 hour EC50 _{growth rate} = 120 mg/L 72 hour NOEC _{biomass} = 21 mg/L 72 hour LOEC _{biomass} = 37 mg/L 72 hour EC50 _{biomass} = 48 mg/L	5
	OECD202	48 hour EC50 >120 mg/L 48 hour NOEC = 120 mg/L	6

Study Type	Method	Result	Ref
Acute toxicity to the giant water flea (crustacean) <i>Daphnia magna</i>			
Fish early-life stage toxicity with fathead minnow, <i>Pimephales promelas</i>	OECD210	32 day NOEC = 1.0 mg/L 32 day LOEC > 1.0 mg/L based on hatch, survival, standard length, and dry weight	7
Long-term toxicity to <i>Daphnia magna</i>	OECD211	21 day NOAEC = 10 mg/L based on reproduction and length	8
Long-term toxicity to the sediment dwelling midge, <i>Chironomus riparius</i>	OECD218	28 day NOEC = 150 mg/kg dry sediment 28 day LOEC > 150 mg/kg dry sediment, based on emergence, development rate and sex ratio	9

EC50 the concentration of the test substance that results in a 50% effect

NOEC no observed effect concentration

NOAEC no observed adverse effect concentration

LOEC lowest observed effect concentration

PNEC (Predicted No Effect Concentration)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the results from the chronic toxicity to fathead minnow (*Pimephales promelas*), the most sensitive species, and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 10).

$$\text{PNEC} = 1000/10 \text{ } \mu\text{g/L} = 100 \text{ } \mu\text{g/L}$$

Environmental risk classification (PEC/PNEC ratio)

$$\text{PEC} = 0.0032 \text{ } \mu\text{g/L}$$

$$\text{PNEC} = 100 \text{ } \mu\text{g/L}$$

$$\text{PEC/PNEC} = 3.2 \times 10^{-5}$$

The PEC/PNEC ratio is < 0.1 which justifies the phrase: 'Use of dapagliflozin has been considered to result in insignificant environmental risk'.

In Swedish: "Användning av dapagliflozin har bedömts medföra försumbar risk för miljöpåverkan" under the heading "Miljörisk".

Environmental Fate Data

Study Type	Method	Result	Ref
Aerobic biodegradation	OECD301F	11% after 28 days.	11

Study Type	Method	Result	Ref
		Not readily biodegradable	
Adsorption/desorption to sludge	OPPTS guideline 835.1110	$K_{d(ads)} = 51 \text{ L/Kg}$ $K_{oc} = 138 \text{ L/Kg}$	12
Aerobic transformation in aquatic sediment systems	OECD308	<ul style="list-style-type: none"> • Mass balance 83-120% of applied radioactivity • The half-lives (DT50) in the water 6.0 - 8.7 days • The half-lives (DT50) in the sediment ranged 95 - 128 days • Extensive mineralisation (^{14}C O_2 formation) observed in both high and low organic matter vessels with 35 and 68% of the applied radioactivity after 99 days • $K_{d(\text{sediment})} = 12 \text{ kg/L}$, based on measured partitioning at 8 days 	13

K_d Distribution coefficient for adsorption

K_{oc} Organic carbon normalized adsorption coefficient

Biotic degradation

Dapagliflozin is not readily biodegraded as measured in an OECD 301F study (Ref 11), but based on the Aerobic Transformation in Aquatic Sediment System OECD 308 (Ref 12), dapagliflozin slowly degrades in the environment.

The degradation of dapagliflozin in aquatic sediment systems was assessed according to the OECD 308 Test Guideline. In this test two different sediments were used, one with high organic matter (HOM) and one with low organic matter content (LOM). Radiolabelled test substance was dosed into the overlying water and the subsequent dissipation from the water phase, and partitioning and/or degradation in the sediment, was observed over a 99 day test period. Since mineralisation was very strong the test vessels were kept to monitor CO_2 production over 148 days.

The partitioning of dapagliflozin in aquatic sediment systems appears to stop at Day 8 and no further significant amounts of radioactivity moved into the sediment. Afterwards degradation and mineralisation took place, apparently in the water phase.

Transformation of dapagliflozin into a possible seven transformation products was rapid as was partitioning to the sediment. Extensive mineralisation was seen in both the high and low organic matter sediment vessels with 35 and 68%, respectively of the applied radioactivity produced as CO² after 99 days.

Following extensive sediment extration, using a variety of organic solvents of varying polarity, a significant proportion of the applied radioactivity, 44% in the high organic matter system and 24% in the low organic matter system, on Day 99, remained as non-extractable residue (NER). At Day 99 the amount of applied radioactivity removed from the total system as ¹⁴CO₂ and NER, accounted for 79 and 92% in the high and low organic matter sediment vessels, respectively. Accordingly the half life of dapagliflozin in both aquatic sediment systems is <120 days.

Based on the data above dapagliflozin has been assigned the risk phrase: 'Dapagliflozin is slowly degraded in the environment.'

In Swedish: "Dapagliflozin bryts ned långsamt i miljön." under the heading "Nedbrytning".

Bioaccumulation

Dapagliflozin is not ionisable within the environmentally relevant pH range (estimated pKa = 12.6). The octanol-water partition coefficient was 2.34, measured at pH 7.4. Since Log P_{ow} < 4, dapagliflozin has low potential to bioaccumulate and the phrase "Dapagliflozin has low potential for bioaccumulation" is assigned.

In Swedish: "Dapagliflozin har låg potential att bioackumuleras" under the heading "Bioackumulering".

Physical Chemistry Data

Study Type	Method	Result	Ref
Octanol-water distribution coefficient	OECD107, Shake flask	log P _{ow} = 2.34 at pH 7	14
Water solubility	OECD105, Shake flask	pH 5 = 720 mg/L pH 7 = 538 mg/L pH 9 = 946 mg/L	15
Hydrolysis	OECD111	<10% after 5 days at 50°C (pH 5 & 7) 11.5 % after 5 days at 50°C (pH 9) t _{1/2} at 25°C ≥ 1 year	16

References

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