FASS

Xigduo

AstraZeneca

Filmdragerad tablett 5 mg/850 mg
(Bruna, bikonvexa, 9,5 x 20 mm ovala, filmdragerade tabletter med ”5/850” präglat på ena sidan och ”1067” präglat på andra sidan)

Diabetesmedel, Perorala blodglukossänkande medel, kombinationer

Aktiva substanser (i bokstavsordning):
Dapagliflozin
Metformin

ATC-kod:
A10BD15

Läkemedel från AstraZeneca omfattas av Läkemedelsförsäkringen .

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

PEC/PNEC = 0.0032/100 = 3.2×10^{-5}
PEC/PNEC ≤ 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 (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100)$

PEC (µg/L) = $1.37*10^{-6}*A*(100-R)$

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 = $10 *10^{6}$
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 = $1.37 * 10^{-6} * 23.54 * (100-0) = 0.0032$ µg/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
	OECD201		5

Study Type	Method	Result	Ref
Toxicity to green algae, *Pseudokirchinella subcapitata*, growth inhibition test		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	
Acute toxicity to the giant water flea (crustacean) *Daphnia magna*	OECD202	48 hour EC50 >120 mg/L 48 hour NOEC = 120 mg/L	6
Fish early-life stage toxicity with fathead minnow, *Pimephales promelas*	OECD210	32 day NOEC = 1.0 mg/L 32 day LOEC > 1.0 mg/L based on hatch, survival,	7

Study Type	Method	Result	Ref
		standard length, and dry weight	
Long-term toxicity to *Daphnia magna*	OECD211	21 day NOAEC = 10 mg/L based on reproduction and length	8
Long-term toxicity to the sediment dwelling midge, *Chironomus riparius*	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).

PNEC = 1000/10 µg/L = 100 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC = 0.0032 µg/L
PNEC = 100 µg/L

PEC/PNEC = 3.2×10^{-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. Not readily biodegradable	11
Adsorption/desorption to sludge	OPPTS guideline 835.1110	$K_{d(ads)}$ = 51 L/Kg K_{oc} = 138 L/Kg	12
Aerobic transformation in aquatic	OECD308	• Mass balance	13

Study Type	Method	Result	Ref
sediment systems		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 ($^{14}CO_2$ formation) observed in both high and low organic matter vessels with 35 and 68% of the applied	

Study Type	Method	Result	Ref
		radioactivity after 99 days • $Kd_{sediment}$ = 12 kg/L, based on measured partitioning at 8 days	

Kd Distribution coefficient for adsorption
Koc 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 CO2 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 CO^2 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 $^{14}CO_2$ 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) t½ at 25°C ≥ 1 year	16

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