FASS

Zomig®

M ℞ (F)

Grunenthal Sweden

Filmdragerad tablett 2,5 mg
(runda, bikonvexa, gula, märkta Z på ena sidan, 8,6 mm)

Medel mot migrän

Aktiv substans:
Zolmitriptan

ATC-kod:
N02CC03

Läkemedel från Grunenthal Sweden omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Zolmitriptan

Miljörisk: Användning av zolmitriptan har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Zolmitriptan bryts ned i miljön.
Bioackumulering: Zolmitriptan har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 1.15 x 10^{-3} µg/L/100 µg/L = 1.15 x 10^{-5}
PEC/PNEC ≤ 0.1

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is based on following data:

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

PEC (µg/L) = 1.5*10^{-6}*A*(100-R)

A (kg/year) = total sold amount API in Sweden year 2019, data from IQVIA
R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization,
hydrolysis or biodegradation) = 0 if no data is available.
P = number of inhabitants in Sweden = 9 *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).

A = 7.66 kg

R = 0

$PEC = 1.5 * 10^{-6} * 7.66 * (100-0) = 1.15 \times 10^{-3}$ µg/L

Ecotoxicity data

Endpoint	Species	Common Name	Method	Time	Result	Ref.
ErC50 - Based on Growth	*Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capri-cornutum*)	Green Alga	OECD 201	72 h	160 mg/L	2
NOEC - Based on Growth					100 mg/L	
LOEC - Based on Growth					320 mg/L	
E_BC50 - Based on Biomass					90 mg/L	
NOEC - Based on Biomass					32 mg/L	
LOEC - Based on Biomass					56 mg/L	
EC50 - Based on Immobilisation	*Daphnia magna*	Giant Water Flea	US FDA Technical Assistance	48 h	250 mg/L	3

Endpoint	Species	Common Name	Method	Time	Result	Ref.
NOEC - Based on Immobilisation & Abnormality			Document 4.08		130 mg/L	
LOEC - Based on Overall Endpoints	*Daphnia magna*	Giant Water Flea	OECD 211	21 d	33 mg/L	4
NOEC - Based on Overall Endpoints				21 d	10 mg/L	
NOEC - Based on Overall Endpoints	*Chironomus riparius*	Midge	OECD 218	28 d	100 mg/kg dry weight	5
LOEC - Based on Overall Endpoints					320 mg/kg dry weight	
NOEC - Based on Overall	*Pimephales promelas*	Fathead Minnow	OECD 210	32 d	1.0 mg/L	6

Endpoint	Species	Common Name	Method	Time	Result	Ref.
Endpoints						
LOEC - Based on Overall Endpoints			OECD 210		>1.0 mg/L	
EC50 - Based on Activated Sludge Respiration Inhibition	-	-	OECD 209	30 min	1728 mg/L	7
EC50 - Based on Activated Sludge Respiration Inhibition			OECD 209	3 h	1080 mg/L	

PNEC (Predicted No Effect Concentration)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. The PNEC is based on the early life stage to fathead minnow (*Pimephales promelas*), the most sensitive species, and an

assessment factor of 10 is applied, in accordance with EMA guidance (Ref. 8).

PNEC = 1000/10 µg/L = 100 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 1.15 x 10^{-3} µg/L/100 µg/L = 1.15 x 10^{-5} i.e. PEC/PNEC ≤ 0.1, thus the risk phrase
'Use of zolmitriptan has been considered to result in insignificant environmental risk' is assigned.

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

Environmental Fate Data

Endpoint	Method	Test Substance Concentration	Time	Result	Ref.
Distribution Coefficient Octanol Water	OECD 107	1000 mg/L	-	Log D = -1.20 @ pH 5 Log D = -1.29 @ pH 7 Log D = 0.84 @ pH 9	9

Endpoint	Method	Test Substance Concentration	Time	Result	Ref.
Percentage Mineralisation	US FDA Technical Assistance Document 3.11 OECD 301B	< 10 mg Carbon/L	28 d	1 %	10
Percentage Mineralisation	US FDA Technical Assistance Document 3.12	0.64 mg Carbon / kg soil	76 d	28.7% in Sandy Loam Soil 14.3% in Sandy Clay Loam Soil 18.8 % in Loamy Soil	11
Biodegradation Half-life			-	T1/2 = 192 d in Sandy Loam Soil T1/2 = 388 d in Sandy Clay Loam Soil	

Endpoint	Method	Test Substance Concentration	Time	Result	Ref.
				T1/2 = 225 d in Loamy Soil	
Dissipation Half-Life	OECD 308	0.1 mg/L (Nominal)	-	T1/2 <2 d in High Organic Matter Sediment & Water. T1/2 <14 d in Low Organic Matter Sediment & Water	12
Mineralisation Half-life				T1/2 = 220 d in High Organic Matter Sediment & Water. T1/2 = 116 d in Low Organic Matter	

Endpoint	Method	Test Substance Concentration	Time	Result	Ref.
				Sediment & Water	
Percentage Hydrolysis	OECD 111	-	120 h	<10% @ pH 5 or 7 28% @ pH 9	13
Hydrolysis Half-Life	-	-	-	T1/2 ≥1 year (Estimated) @ pH 5 or 7	

Biotic degradation

Zolmitriptan is not readily biodegradable (ref 11) and is hydrolytically stable (ref 13). However, it is predicted to degrade within aquatic sediment systems (ref 12). In both test systems (high and low organic carbon), zolmitriptan was rapidly lost from the aqueous phase through dissipation into the sediment phase and degradation. The dissipation half-lives from the water being <2 days in the high organic carbon test system, and <14 days in the low organic carbon test system. The following extraction scheme was used:

Time-point (Day of sampling)	1st extraction	2nd extraction	3rd extraction	4th extraction	5th extraction
			% of applied radioactivity		

0	Acetone + 5% ammonia	NA	NA	NA	NA
2	Acetone + 5% ammonia	NA	NA	NA	NA
6	Acetone + 5% ammonia	SDS at 24 g/L + 5% ammonia	SDS at 24 g/L + 5% ammonia	SDS at 24 g/L + 5% ammonia	NA
14	RO water	Acetone + 5% ammonia	SDS at 24 g/L + 5% ammonia	SDS at 24 g/L + 5% ammonia	SDS at 24 g/L + 5% ammonia
42	THF + 5% ammonia	THF + 5% ammonia	SDS at 24 g/L in RO water	SDS at 24 g/L in RO water	NA
99	THF + 5% ammonia	SDS at 24 g/L in THF + 5% ammonia	SDS at 24 g/L in THF + 5% ammonia	NA	NA

SDS: sodium dodecyl sulphate, THF: tetrahydrofuran, RO water: reverse osmosis water, NA: not applicable (not performed)

Despite considerable attempts to extract this radioactivity, on Day 99, 60 and 32% of the applied radioactivity remained bound to the sediment residue in the high and low organic sediments, respectively. A large amount of mineralisation was observed in both test systems. The mineralisation half-lives were 116 days in the low organic carbon test system, and 220 days high organic carbon test system.

Critically, specific zolmitriptan analysis of sediment and overlying water samples indicated that even at day 0 the extractable radioactivity present as zolmitriptan in overlying water and sediment combined was equivalent to 42 and 47% of applied radioactivity in the high and low organic matter systems respectively.

Day 14 Water Phase:
By day 14 total radioactivity in the overlying water was equivalent to 21 and 32 % of applied radioactivity in high and low organic carbon systems respectively. However, no further specific zolmitriptan analysis is available from the water phase, thus it could be conservatively assumed that 100% of the radioactivity present is therefore attributable to zolmitriptan.

Day 14 Sediment Phase:
In the sediment extracts specific zolmitriptan analysis was conducted throughout the study. At day 14, the specific analysis indicated that 4 and 2 % of applied radioactivity was attributable to zolmitriptan in high and low organic carbon sediments respectively.

Therefore, even considering a highly conservative view that 100% of the measured radioactivity in the overlying water at day 14 remained as zolmitriptan (unlikely given day 0 results), the total system radioactivity attributable to zolmitriptan would be equivalent to 25 and 34 % of the applied radioactivity in high and low organic carbon systems respectively at day 14.

In this case, the total system half-life was not reported; however, as detailed above, the report shows that total amount of radioactivity, attributable to zolmitriptan in the water and sediment

extract combined, is <50% after 14d in both the high- and low-organic carbon test systems. The Fass.se guidance indicates that the persistence criteria should be based on loss of parent material and therefore both water/sediment systems would fulfil the <32d DT_{50} criteria (Table 7 in Ref 1).

The data produced in this study show that Zolmitriptan was degradable in both test systems.
Therefore, it is considered justified to assign this substance the risk phrase: ‘Zolmitriptan is degraded in the environment’.

In Swedish: “Zolmitriptan bryts ned i miljön.” under the heading “Nedbrytning”.

Bioaccumulation

The Log D was determined at different pH values (Ref 9):

pH	Log D
5	-1.20
7	-1.29
9	0.84

Since Log D < 4, zolmitriptan has low potential to bioaccumulate and the phrase ‘Zolmitriptan has low potential for bioaccumulation’ is assigned.

In Swedish: “Zolmitriptan har låg potential att bioackumuleras” under the heading “Bioackumulering”.

Physical Chemistry Data

Endpoint	Method	Test Conditions	Result	Ref.
Dissociation Constant	Potentiometric Method	-	pKa = 9.64	8
Solubility Water	OECD 105	pH 5, 7 or 9	>1300 mg/L	14
Soil Adsorption Coefficient	US FDA Technical Assistance Document 3.08	Sandy Loam Soil, pH 6.7	Koc = 1296	15
		Sandy Clay Loam Soil, pH 5.4	Koc = 1962	
		Loamy Soil, pH 6.1	Koc = 1431	
Soil Distribution Coefficient		Sandy Loam Soil, pH 6.7	Kd = 27.2	
		Sandy Clay Loam Soil, pH 5.4	Kd = 43.2	
		Loamy Soil, pH 6.1	Kd = 133	

Metabolism

Over 60% of a single oral dose is excreted in the urine (mainly as the indoleacetic acid metabolite) and about 30% in faeces mainly as unchanged parent compound (ref 16).

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