FASS

Noxafil

MSD

Enterotablett 100 mg
(Guldragerad, kapselformad tablett 17,5 mm lång märkt med ”100” på ena sidan)

Antimykotika för systemiskt bruk, triazolderivat

Aktiv substans:
Posakonazol

ATC-kod:
J02AC04

Läkemedel från MSD omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Posakonazol

Miljörisk: Användning av posakonazol har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Posakonazol bryts ned i miljön.
Bioackumulering: Posakonazol 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*109*(100-R))/(365*P*V*D*100) = $1.5*10^{-6}$*A(100-R)

PEC = 0.003 µg/L

Where:
A = 18.35 kg (total sold amount API in Sweden year 2015, data from IMS Health).
R = 0 % removal rate (worst case assumption)

P = number of inhabitants in Sweden = $9 * 10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. I)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Crustacean, water flea (Daphnia magna):
Acute toxicity (OECD 202) (Ref.II)
EC50 48 h (immobility, mortality) = 276 µg/L

Chronic toxicity (OECD 211) (Ref. III)
EC50 21 day (immobility, reproduction) > 244 µg/L
NOEC 21 d (growth, reproduction) = 244 µg/L
No effects seen at highest concentration tested

Fish, rainbow trout (Oncorhynchus mykiss):
Acute toxicity (OECD 203) (Ref. IV)
LC50 96 h (mortality) > 950 µg/L
NOEC = 950 µg/L
No effects seen at highest concentration tested

Fish early life stage, fathead minnow (Pimephales promelas):
Chronic toxicity (OECD 210) (Ref. V)
NOEC 33 d (growth) = 206 µg/L

Algae, green algae (Selenastrum capricornutum) (OECD 201) (Ref. VI):
EC50 96 h (cell density) = 189 µg/L
EC50 96 h (biomass) = 255 µg/L
EC50 96 h (growth rate) > 509 µg/L
NOEC 96 h (cell density, biomass, growth rate) = 41 µg/L

PNEC = 4.1 µg/L (41µg/L / 10 based on the most sensitive chronic NOEC for *Selenastrum capricornutum* with an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.003/4.1 = 6.7E-04, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of posaconazole has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Sediment Transformation: The total system half-life = 0.7 to 13.3 days (OECD 308) (Ref VII)

Test systems were dosed with 14C-labeled posaconazole at a nominal concentration of 200 ug/L in the water layer. Test systems were incubated in the dark at approximately 20 ºC for up to 103 days, and maintained under aerobic conditions by gently bubbling air into the water layers. Effluent gasses were passed through charcoal sorbent tubes to trap organic volatiles, followed by alkali solutions to trap evolved carbon dioxide. Duplicate test chambers of each sediment-water type were sacrificed on days 0, 2, 5, 14,

28, 56 and 103. Water layers and sediment layers were extracted and analyzed for total radioactivity by liquid scintillation counting (LSC). The mean percent of applied radioactivity in each fraction is presented in the following table:

Test System	Interval (Days)	Water Layers	Sediment Layers	Gases	Material Balance (Recovery)
Brandywine Creek	0	95.3%	2.0%	--	97.3%
	2	56.7%	41.6%	0.0%	98.2%
	5	36.0%	64.2%	0.0%	100.2%
	14	23.1%	72.3%	0.0%	95.4%
	28	15.8%	84.9%	0.0%	100.8%
	56	11.7%	86.6%	0.0%	98.3%
	103	8.6%	91.6%	0.0%	100.3%
Choptank River	0	97.0%	3.3%	--	100.3%
	2	80.2%	22.2%	0.0%	102.4%
	5	68.8%	33.8%	0.0%	102.6%
	14	27.7%	71.7%	0.1%	99.5%
	28	32.5%	64.7%	0.0%	97.2%
	56	26.7%	68.1%	0.0%	94.8%
	103	19.6%	74.9%	0.2%	94.7%

Extracts from water and sediment layers were analyzed by HPLC for parent test substance and radiolabeled transformation products. The mean percent of applied radioactivity in the samples is presented in the following table:

		Water Layers				Sediment Extracts		
Test System	Interval (Days)	Parent Posaconazole	Trans.1 Prod.	Total % of Dose		Parent Posaconazole	Trans.1 Prod.	Total % of Dose
Brandywine Creek	0	87.9%	7.4%	95.3%		NA[2]	NA[2]	NA[2]
	2	6.7%	50.0%	56.7%		3.5%	29.3%	32.8%
	5	3.7%	32.3%	36.0%		4.9%	40.2%	45.1%
	14	1.3%	21.8%	23.1%		2.7%	45.7%	48.5%
	28	0.8%	15.1%	15.8%		1.4%	48.7%	50.1%
	56	0.0%	11.7%	11.7%		0.3%	46.6%	47.0%
	103	0.0%	8.6%	8.6%		0.0%	45.2%	45.2%
Choptank River	0	94.4%	2.6%	97.0%		NA[2]	NA[2]	NA[2]
	2	65.8%	14.3%	80.2%		13.0%	8.4%	21.4%
	5	47.1%	21.7%	68.8%		15.9%	15.2%	31.1%
	14	6.4%	21.3%	27.7%		21.8%	45.3%	67.2%
	28	9.1%	23.4%	32.5%		29.3%	30.2%	59.5%
	56	0.3%	26.4%	26.7%		3.0%	48.8%	51.8%

	103	0.2%	19.4%	19.6%		2.7%	46.5%	49.2%

1 Trans. Prod. = transformation products

2 NA = not analyzed (sediment layers were not extracted on day 0)

Posaconazole disappeared rapidly from the water layers in both test systems by transformation and by partitioning to the sediment layers. The half-lives for Posaconazole were 0.5 and 4.5 days from the Brandywine Creek and Choptank River water layers, respectively.

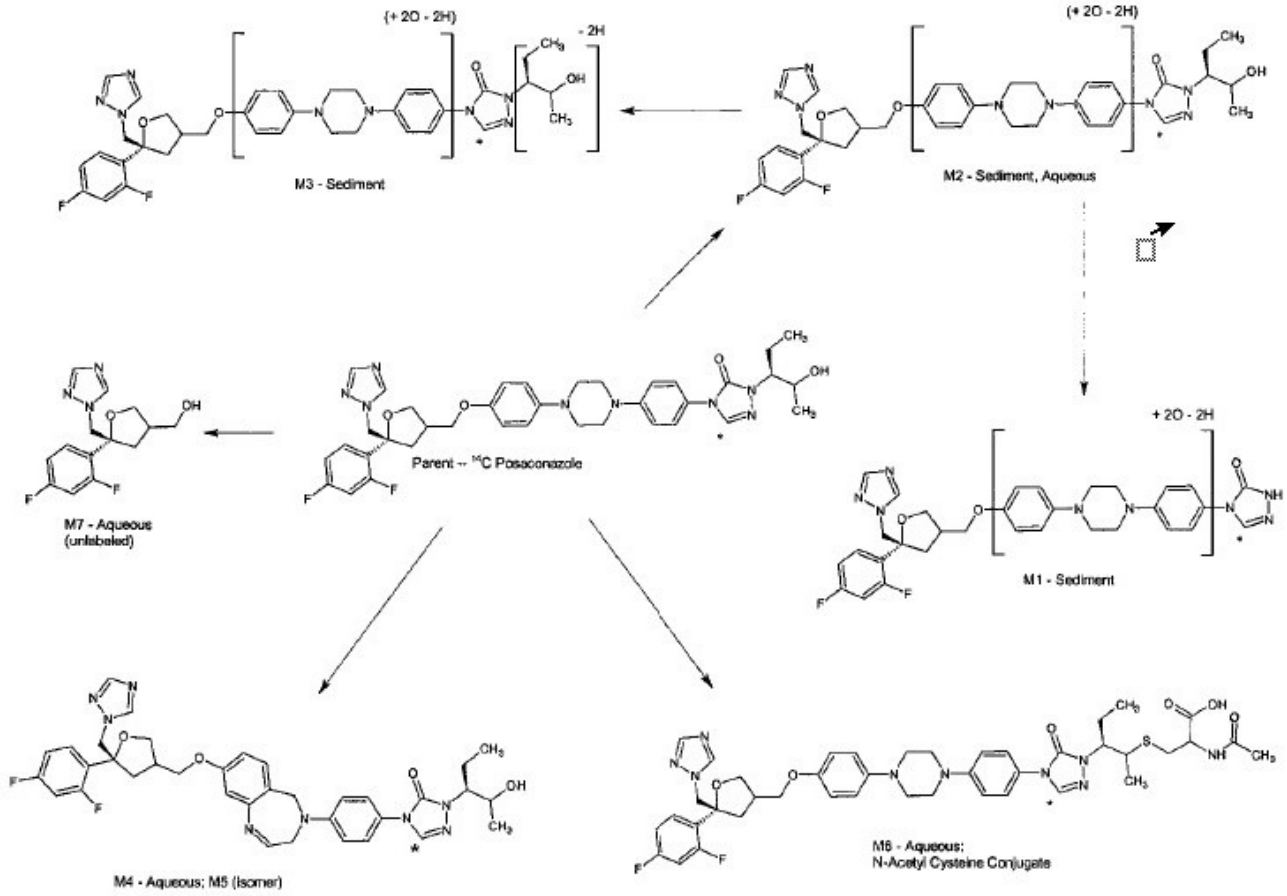
The mean amounts of posaconazole in the sediment layers increased to a maximum of 4.9% on day 5 in Brandywine Creek samples and 29.3% on day 28 in Choptank River samples. The mean amounts of posaconazole in the total test systems (i.e. water layers extracts plus sediment extracts) at the end of the test were 0.0% and 2.9%, respectively. The half-lives for posaconazole in the total test systems were 0.7 and 13.3 days, respectively.

Through all test intervals, the mean maximum percentages of applied radioactivity recovered as transformation products were 79% on day 2 in Brandywine Creek samples and 75% on day 56 in Choptank River samples. The mean amount of radiolabeled residues that could not be extracted from the sediment layers at the end of the test were 46.5% and 25.7%, respectively. The mean maximum cumulative amount of mineralization or ultimate biodegradation observed from all test jars was <0.5% for both test systems. Total mean recoveries ranged from 94.7% to 102.6% throughout the study.

The calculated half-life of posaconazole and degradates are presented in the following table:

	Half-life (days)	
	Choptank River	Brandywine River
Parent Posaconazole	20.4	21.1
M2	38.0	106.7
M3	358.1	108.1

The overall postulated transformation/metabolism scheme for posaconazole in river waters and sediments in show below.



Justification of chosen degradation phrase:
Posaconazole has a half-life less than 32 days. The phrase “Posaconazole is degraded in the environment” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Posaconazole has a measured bioconcentration factor (BCF) of 20 (OECD 305) (Ref VIII).

Justification of chosen bioaccumulation phrase:
Since the BCF < 500, the phrase “Posaconazole has low potential for bioaccumulation” is chosen.

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.html
II. Wildlife International, Ltd. 2003. "Posaconazole (SCH 56592): A 48-Hour Flow-Through Acute Toxicity Test with the Cladoceran (Daphnia magna)," Study No., 554A-101, WIL, Easton, MD, USA 14 July 2003.
III. Wildlife International, 2011. "Posaconazole: A Flow-Through Life-Cycle Toxicity Test with the Cladoceran (Daphnia magna)," Project No. 105A-199A, WIL, Easton, MD, 08 November 2011.
IV. Wildlife International, Ltd. 2003. "Posaconazole (SCH 56592): A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss)," Study No., 554A-102, WIL, Easton, MD, USA 14 July 2003.
V. Wildlife International, 2012. "Posaconazole: An Early Life Stage Toxicity Test with the Fathead Minnow (Pimephales promelas)," Project No. 105A-200, WIL, Easton, MD, 14 March 2012.

VI. Wildlife International, Ltd. 2003. "Posaconazole (SCH 56592): A 96-Hour Toxicity Test with the Freshwater Alga (Selenastrum capricornutum)," Study No., 554A-103A, WIL, Easton, MD, USA 15 July 2003.
VII. Wildlife International, 2012. "Posaconazole: Aerobic Transformation in Aquatic Sediment Systems," Project No. 105E-158, WIL, Easton, MD, 05 December 2012.
VIII. Wildlife International, 2012. "Posaconazole: A bioconcentration test with the Bluegill (Lepomis macrochirus)," Project No. 105A-203, WIL, Easton, MD, 16 October 2012.