FASS

ADCIRCA

MRx EF

Lilly

Filmdragerad tablett 20 mg
(Tillhandahålls ej) (orange, mandelformad tablett, märkt "4467" på ena sidan, 7,4 x 12,1 mm)

Medel mot pulmonell arteriell hypertension

Aktiv substans:
Tadalafil

ATC-kod:
G04BE08

Läkemedel från Lilly omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Tadalafil

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

Detaljerad miljöinformation

ENVIRONMENTAL RISK CLASSIFICATION
Predicted Environmental Concentration (PEC)
PEC (µg/L) = (A x 1000000000 x (100 – R)) ÷ (365 x P x V x D x 100)
= 0,0000015 x A x (100 – 0)
= 0,0000015 x 12,437171238765 x 100
= 0,0019 µg/L
Where:
A = 12,437171238765 kg (total amount sold in Sweden in 2020, data from IQVIA). This number is not adjusted for metabolism.
R = 0% removal rate in a sewage treatment plant
P = 9000000 population of Sweden

V = 200 L of wastewater per capita per day (ECHA 2016)
D = 10, dilution of wastewater by surface water flow (ECHA 2016)

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Species	Study Description and Results	Study Number	Guideline
Algae *Pseudokirchneriella subcapitata*	72 hour exposure Average specific growth rate: EC50growth rate: >1200 µg/L NOECgrowth rate: 1200 µg/L Yield*: EC50yield: >1200 µg/L NOECyield: 300 µg/L	1982.6290 (2008)	OECD 201
Crustacean *Daphnia magna* (acute)	48 hr immobilization EC50: >2000 µg/L NOEC: 2000 µg/L	303/687 (1995)	OECD 202
Crustacean *Daphnia magna* (chronic)	Full Life-Cycle Toxicity Test (21 days), reproduction, survival, growth NOEC: 480 µg/L	1982.6284 (2008)	OECD 211
Fish, Rainbow trout (*Oncorhynchus mykiss)* (acute)	96 hr acute toxicity LC50: >2100 µg/L NOEC: 2100 µg/L	F00999 (2009)	FDA 4.11
Fish, Fathead Minnows (*Pimephales promelas*) (chronic)	Early Life Stage Toxicity Test (embryo + 28 days post hatch) NOEC: 1200 µg/L	1982.6283 (2008)	OECD 210

Abbreviations: EC50 = median effective concentration, LC50 = median lethal concentration, NOEC = no-observed-effect concentration.
*While endpoints derived for yield (biomass) are included, only growth rate endpoints will be considered for classification, since growth rate is the preferred observational endpoint (ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b 2016).

Calculation of PNEC
PNEC = 480 µg/L ÷ 10
PNEC = 48 µg/L
The PNEC was calculated from the NOEC of the most sensitive species, daphnia, divided by an assessment factor of 10. An assessment factor of 10 was used since chronic data are available for algae, crustaceans and fish.

PEC/PNEC Ratio
PEC/PNEC = 0,0019 ÷ 48 = 0,00004

The PEC/PNEC ratio of less than 0.1 justifies the phrase “Use of tadalafil has been considered to result in insignificant environmental risk.”

DEGRADATION CLASSIFICATION

Biotic Degradation

Ready degradability:

Tadalifil has not been tested for ready biodegradability. However, tadalafil is assumed to be not readily biodegradable given the small amount of $^{14}CO_2$ evolved (~5% of applied radioactivity) when ^{14}C-tadalafil was incubated with sewage sludge for 85 days (Study 1982.6287, OECD 302A, a test of inherent degradability).

Inherent degradability:

Tadalafil is transformed (DT50 = 9 days) to more polar hydroxylated metabolites when incubated with activated sewage sludge under aerobic conditions (SCAS test, modified from OECD 302A; Study 1982.6287).

Simulation study:

Tadalafil was transformed in two water-sediment systems in which radiolabelled tadalafil was incubated under aerobic conditions for 108 days (OECD 308; Study 1982.6288). Parent tadalafil disappeared from the overlying water with a DT50 of approximately 4 days. Dissipation of tadalafil was due to partitioning to sediment and to primary and ultimate degradation. The sediment was extracted three times with solvent systems of varying polarity (1. Acetonitrile, 2. Acetonitrile:water 80:20, 3. Acetonitrile:water:hydrochloric acid 80:20:0.1 v:v) and the pooled extract was characterized for parent and transformation products. By the end of the study, several polar transformation products were observed and 1,8% and 3,4% of the applied radioactivity evolved as $^{14}CO_2$ over the 108 day study. Approximately 25% and 30% of the radioactivity could not be extracted from the sediment. The calculated half-lives for dissipation of tadalafil from the whole system (via degradation and irreversible binding to sediment) were 70 and 117 days.

Abiotic Degradation

Tadalafil is stable with respect to hydrolysis (OECD 111; Study 1982.6281). Based on the lack of observed degradation in the algae toxicity study (Study 1982.6290) under continuous light conditions for 72 hours, tadalafil is stable with respect to photolysis.

Justification of the degradation phrase:

Tadalafil disappeared from water sediment systems with half-lives of 70 and 117 days and there was evidence of biotransformation and mineralization. Therefore, the degradation phrase “Tadalafil is slowly degraded in the environment” is based on the fate in water-sediment systems.

Bioaccumulation

Partition coefficient:

The octanol/water partition coefficient of 2,32 was determined using an HPLC correlation method (EEC Method A8, Study 303/688). As tadalafil has no ionizable groups, this value is appropriate over an environmentally relevant range of pH. As the log K_{ow} is less than 3 and the compound is subject to extensive metabolism, tadalafil is not expected to bioaccumulate in biotic tissues.

Justification of chosen bioaccumulation phrase:

The octanol-water partition coefficient is less than 4, justifying the use of the phrase “Tadalafil has low potential for bioaccumulation.”

Excretion (metabolism)

In humans, tadalafil is transformed into metabolites that are at least 45 times less potent based on *in vitro* phosphodiesterase 5 inhibition. Based on quantification of residue excretion in humans, one-third, at most,

of the total dose is excreted as tadalafil. Thus, human metabolism can be estimated to reduce the amount of tadalafil that reaches the sewage treatment facility by at least two-thirds. For this risk assessment, however, a worst-case total residues approach will be taken; that is, tadalafil and its human metabolites will be considered to have the same activity.

PBT/vPvB ASSESSMENT

Although a bioconcentration factor has not been empirically determined, tadalafil is not considered bioaccumulative because the log octanol-water partition coefficient value is less than 4 and because tadalafil is subject to metabolism. The chronic aquatic NOEC values are all greater than 10 µg/L. The effects of tadalafil in mammals have been summarized elsewhere. The pharmacological target of tadalafil in mammals is not a hormone receptor. Because tadalafil does not meet the criteria for bioaccumulative or toxicity, it is not considered to be PBT or vPvB.

References

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Eli Lilly and Company Safety Data Sheet. 04 November 2015. Cialis®. http://ehs.lilly.com/msds/Cialis.pdf

Study 1982.6287. 2008. [^{14}C]Tadalafil (^{14}C-LY450190) - Determination of the Inherent Biodegradability and Adsorption by the SCAS Test, Modified from OECD Guideline 302A. Eli Lilly and Company.

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