FASS

YENTREVE®

Lilly

Enterokapsel, hård 40 mg
(En ogenomskinlig, orange underdel märkt ”40 mg” och en ogenomskinlig, blå överdel märkt ”9545”.)

Medel vid ansträngningsinkontinens

Aktiv substans:
Duloxetin

ATC-kod:
N06AX21

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

Miljöpåverkan

Duloxetin

Miljörisk: Användning av duloxetin har bedömts medföra låg risk för miljöpåverkan.
Nedbrytning: Duloxetin bryts ned långsamt i miljön.
Bioackumulering: Duloxetin 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 727,4225603 x 100
= 0.11 µg/l
Where:

A = 727,4225603 kg (total amount of duloxetine sold in Sweden in 2020 as duloxetine, data from IQVIA). This number is not adjusted for metabolism.

API form	Sales in 2020 kg
duloxetine hydrochloride	816,59557281
duloxetine	727,4225603*

*calculated by multiplying the kg of duloxetine hydrochloride sold by the molecular weight ratio of duloxetine free base:duloxetine hydrochloride salt (297.42:333.88)
R = Assumed 0% removal rate in a sewage treatment plant
P = 9000000 population of Sweden
V = 200 litre of wastewater per capita per day (default from ECHA, 2012)
D = 10 dilution of wastewater by surface water flow (default from ECHA, 2012)

Measured Environmental Concentration (MEC)

The Swedish Environmental Research Institute has conducted a national screening program for 101 pharmaceuticals in urban wastewater treatment plants and their receiving waters (Fick et al 2011, 2015). Samples of wastewater treatment plant influent and effluent (total of 39 samples) were analyzed and 11 samples had measurable levels of duloxetine. The measured concentrations of duloxetine ranged from 0.001 to 0.014 µg/l, with a mean concentration of 0.007 µg/l. In surface water no samples had detectable levels of duloxetine, even those downstream of wastewater treatment plant effluents (the limit of quantitation was 0.001 µg/l). The data reported by Fick et al (2011, 2015) are in agreement with previous reports of duloxetine concentrations in U.S. wastewater effluents and receiving surface waters (levels were less than 0.005 and 0.002 µg/l, respectively) in that detections are infrequent and levels are less than 0.01 µg/l (Schultz and Furlong 2008; Schultz et al 2010). Therefore, the calculated PEC of 0.1 µg/l is greater than actual measured concentrations detected in surface water. Nonetheless, the PEC of 0.1 µg/l will be used to assess the environmental risk.

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Algae

- Study 1982.6118 with *Pseudokirchneriella subcapitata* (OECD 201)
  EC50 72 hr (biomass) = 64 µg/l
  EC50 72 hr (growth rate) = 200 µg/l
  NOEC 72 hr = 4.3 µg/l

Crustacean (Daphnids)

Acute toxicity

- Study 1982.6116 with *Daphnia magna* (OECD 202)
  EC50 48 h (immobilization) = 2400 µg/l

Chronic toxicity

- Study 1982.6129 with *Daphnia magna* (OECD 211)
  NOEC 21 days (survival, reproduction, growth) = 11 µg/l

Fish

Acute toxicity

- Study 1982.6125 with *Oncorhynchus mykiss* (OECD 203)
  LC50 96 h (mortality) = 1300 µg/l

Chronic toxicity

- Study 1982.6273 with *Pimephales promelas* (OECD 210)
  NOEC 5 d embryos + 28 d larvae (mortality, growth) = 12 µg/l

Calculation of PNEC

PNEC = 0.43 µg/l
PNEC = lowest NOEC divided by an assessment factor of 10. The NOEC for algae has been used since algae is the most sensitive tested species. An assessment factor of 10 was used because long-term results were available for species from three trophic levels: fish, daphnids and algae.

Environmental risk classification (PEC/PNEC Ratio)

PEC/PNEC = 0.11 ÷ 0.43 = 0.25
The PEC/PNEC ratio of less than 1 but greater than 0.1 justifies the phrase “Use of duloxetine has been considered to result in low environmental risk.”

Degradation

Biotic Degradation

Inherent degradability:
In a biodegradation study based on OECD guideline 302A, radiolabeled duloxetine was incubated with activated sludge inoculum under aerobic conditions at 22 ± 3ºC for 8 days (Study 1982.6123). No significant biodegradation was observed although a small non-duloxetine radioactive peak was noted indicating potential for transformation.

Simulation studies:
The degradation potential of radiolabeled duloxetine was also investigated in two different water-sediment systems over 100 days in aerobic conditions following the OECD 308 guideline (Study 807566). ^{14}C-Duloxetine disappeared from the overlying water with a DT50 of 3 days in both systems. The disappearance from water was due in part to partitioning to the sediment. Duloxetine was also extensively degraded in the water-sediment systems. After 7 days only 48 to 61% of the applied radioactivity was recovered as duloxetine in the total system, and at the end of the study 37 to 58% was recovered as duloxetine, suggesting that biodegradation is rapid initially and then plateaus. The half-lives for disappearance of duloxetine from the total water-sediment system for the two different systems were 78.2 and 240.7 days. By the end of the study, up to 45 separate degradation products were observed. The majority of the degradation products were less than 2% of applied radioactivity. At their maximum occurrence, four of the products were observed to be 5 to 21% of the applied radioactivity, but these levels had decreased to less than 5% by Day 100. At the end of the study, approximately 21 to 32% of the applied radioactivity was unextractable, despite extensive extraction procedures including ethanol, acetone/formic acid, methanol/formic acid, and methanol/dichloromethane. The unextractable residues were not considered to be bioavailable. Additionally, there was evidence of ultimate degradation over the course of the study. At Day 7, 0.4 to 1% of the applied radioactivity evolved as radiolabelled CO_2. By the end of the study, evolved $^{14}CO_2$ accounted for 5 to 11% of the applied radioactivity.

Abiotic Degradation

Hydrolysis:

In a hydrolysis study (based on OECD guideline 111), duloxetine hydrolyzed slowly with a half-life ranging from 1,5 to 3,5 months at 30°C (Study 1982.6120).

Photolysis:
Photolysis of duloxetine in the aqueous environment is likely based on its ultraviolet-visible adsorption (Study 1982.6130) and empirical evidence from the algae toxicity study (1982.6118, OECD 201). In the algae study, an abiotic control (no algae) sample spiked with duloxetine at 0.029 mg/L had no detectable duloxetine (limit of detection = 0.0034 mg/L) after three days of incubation in continuous light. While duloxetine binds to glass to some degree (there was a 30% decrease in aqueous concentration in a glass test tube after 7 days, Study 1982.6112), the majority of the rapid disappearance is most likely due to photolysis.

Removal during sewage treatment

There is evidence that there will be some removal of duloxetine during sewage treatment due to sorption to sludge solids. Using a batch sorption protocol similar to OECD 106 (Study 1982.6123), the K_d for adsorption of duloxetine to activated sludge ranged from 1166 to 1731 (K_{oc} ranged from 2893 to 4296). Hörsing et al (2011) reported K_d values of 13000 for primary sludge from Denmark and 2900 for secondary sludge from Sweden. However in this classification, no removal during sewage treatment was considered during calculation of the PEC.

Justification of the degradation phrase:
The environmental fate data from the water-sediment degradation study (OECD 308) was used to determine the persistence classification of duloxetine. Since the calculated DT50 in one sediment system was less than 120 days (78,2 days) and the other was greater than 120 days (240.7 days), duloxetine is considered to be slowly degraded in the environment.

Bioaccumulation
Partitioning coefficient:
The log of the octanol-water partition coefficients of duloxetine measured at pH values of 4, 7, and 9 were measured to be 0.781, 1.54, and 3.35, respectively (Study 1982.6127, OECD 107).

Justification of chosen bioaccumulation phrase:
Since the log K_{ow} at pH 7 is less than 4, duloxetine has low potential to bioaccumulate in biotic tissues.

Excretion (metabolism)
Duloxetine is subject to extensive oxidative and conjugative metabolism by humans (Cymbalta package insert; Lantz et al., 2003). Only trace amounts of unchanged duloxetine are excreted and the major metabolites have not been shown to have significant pharmacological activity. Despite this, reduction due to human metabolism was not considered in the estimate of predicted exposure concentration of duloxetine.

PBT/vPvB ASSESSMENT
Because the log Kow is less than 4.5, duloxetine does not meet the REACH criteria for bioaccumulative (ECHA, 2012). Therefore, duloxetine is not classified as PBT or vPvB.

References
ECHA, European Chemicals Agency. 2012 Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment and Chapter R.16: Environmental Exposure Estimation.

Cymbalta Package Insert. http://pi.lilly.com/us/cymbalta-pi.pdf

Cymbalta (32%) Capsules Safety Data Sheet. Revision 09/24/2015. http://ehs.lilly.com/msds/Cymbalta.pdf

Fick J, Lindberg RH, Kaj L, Brorström-Lundén E. 2011. Results from the Swedish National Screening Programme 2010. Subreport 3. Pharmaceuticals. Swedish Environmental Research Institute. IVL Report B2014. 56 pp.

Fick J, Linberg RH, Fång J, Magnér J, Kaj L, Brorström-Lundén E. 2015. Screening 2014 Analysis of pharmaceuticals and hormones in samples from WWTPs and receiving waters. 2015. IVL Swedish Environmental Research Institute. Number C135. 51 pp.

Hörsing M, Ledin A, Grabic R, Fick J, Tysklind M, la Cour Jansen J, Anderson HR. 2011. Determination of sorption of seventy-five pharmaceuticals in sewage sludge. Wat Res 45:4470-4482.

Lantz RJ, Gillespie TA, Rash TJ, Kuo F, Skinner M, Kuan H-Y, Knadler MP. 2003. Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. Drug Disp Metab 31:1142-1150.

Schultz MM, Furlong ET. 2008. Trace analysis of antidepressant pharmaceuticals and their select degradates in aquatic matrices by LC/ESI/MS/MS. Anal Chem 80:1756-1762.

Schultz MM, Furlong ET, Kolpin DW, Werner SL, Schoenfuss HL, Barber LB, Blazer VS, Norris DO, Vajda AM. 2010. Antidepressant pharmaceuticals in two U.S. effluent-impacted streams: Occurrence and fate in water and sediment, and selective update in fish neural tissue. Environ Sci Technol 44:1918-1925.

Lilly Study 1982.6118. 2001. Duloxetine hydrochloride – Acute toxicity to the freshwater green alga *Pseudokirchneriella subcapitata*, following OECD Guideline #201.

Lilly Study 1982.6116. 2001. Duloxetine hydrochloride – Acute toxicity to daphnids (*Daphnia magna*) under static conditions. OECD 202.

Lilly Study 1982.6129. 2001. Duloxetine hydrochloride – Full life-cycle toxicity test with water fleas, *Daphnia magna*, under flow-through conditions following FIFRA Guideline 72-4, OECD Guideline #211, and OPPTS draft guideline 850.1300.

Lilly Study 1982.6125. 2001. Duloxetine hydrochloride – Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) under static-renewal conditions. OECD 203.

Lilly Study 1982.6273. 2007. Duloxetine HCl – Early life-stage toxicity test with fathead minnow (*Pimephales promelas*) following OECD guideline #210.

Lilly Study 1982.6123. 2001. Duloxetine hydrochloride – Determination of the inherent biodegradability and adsorption of a test substance by the SCAS test, modified from OECD guideline 302A.

Lilly Study 807566. 2007. The aerobic transformation of [14C]-duloxetine hydrochloride in aquatic sediment systems. OECD 308.

Lilly Study 1982.6120. 2001. Duloxetine hydrochloride – Determination of the abiotic degradation of the test substance by hydrolysis at three different pH values following OECD guideline 111.

Lilly Study 1982.6130. 2001. Duloxetine hydrochloride – Determination of the ultraviolet-visible absorption spectrum in aqueous solution following OECD proposed guideline for phototransformation of chemicals in water.

Lilly Study 1982.6112. 2001. Duloxetine hydrochloride – Validation of the analytical method for the determination of duloxetine in aqueous solutions.

Lilly Study 1982.6127. 2001. Determining the partitioning coefficient (n-octanol/water) of a test substance by the flask-shaking method following OECD guideline 107.