FASS

Atomoxetin Glenmark

Glenmark Pharmaceuticals Nordic

Kapsel, hård 10 mg

(hård gelatinkapsel storlek 3 (ca 15,7 ± 0,4 mm längd), vit överdel märkt med ”10” och vit underdel märkt med ”mg” i svart bläck)

Psykoanaleptika, centralt verkande sympatomimetika

Aktiv substans:

Atomoxetin

ATC-kod:

N06BA09

Läkemedel från Glenmark Pharmaceuticals Nordic omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för atomoxetin är framtagen av företaget Lilly för Strattera, Strattera®

Miljörisk: Användning av atomoxetin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Atomoxetin är potentiellt persistent.
Bioackumulering: Atomoxetin 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 91,32578008 x 100
= 0,01 µg/l
Where:
A = 91,32578008 kg (total amount of atomoxetine sold in Sweden in 2020 as atomoxetine hydrochloride, data from LIF/IQVIA). This number is not adjusted for metabolism.

API form	Sales in 2020 kg/2020
atomoxetine hydrochloride	104,36435
atomoxetine	91,32578008*

*calculated by multiplying the kg of atomoxetine hydrochloride sold by the molecular weight ratio of atomoxetine free base:atomoxetine hydrochloride salt (255,362:291,82)
R = Assumed 0% removal rate in a sewage treatment plant
P = 9000000 population of Sweden
V = 200 L of wastewater per capita per day (default from ECHA, 2017)
D = 10 dilution of wastewater by surface water flow (default from ECHA, 2017)

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Algae (*Pseudokirchneriella subcapitata*) (OECD 201) (Study 1982.6145)
EC50 72 hr (biomass) 420 µg/l
EC50 72 hr (growth rate) 730 µg/l
NOEC 72 hr = 260 µg/l

Crustacean (*Daphnia magna*)
Acute toxicity (OECD 202) (Study 1982.6143)
EC50 48 h (immobilization) = 5700 µg/l
Chronic toxicity (OECD 211) (Study 1982.6146)
NOEC 21 days (survival, reproduction, growth) = 470 µg/l

Fish
Rainbow trout (*Oncorhynchus mykiss*) (Study 1982.6144)
Acute toxicity (OECD 203)
LC50 96 h (mortality) = 8800 µg/l

Fathead minnow (*Pimephales promelas*)
Chronic toxicity (OECD 210) (Study 1982.6269)
NOEC 5 d embryos + 28 d larvae (mortality, growth) = 32 µg/l

Calculation of PNEC

PNEC = 32 µg/l ÷ 10
PNEC = 3,2 µg/l

The PNEC was calculated from the NOEC for fathead minnows as they are the most sensitive of the species tested in long-term studies. 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 = 0,01 ÷ 3,2 = 0,004

The PEC/PNEC ratio of less than 0,1 justifies the phrase “Use of atomoxetine has been considered to result in insignificant environmental risk.”

Degradation

Biotic Degradation

Inherent degradability:

In a biodegradation study based on OECD guideline 302A, radiolabeled atomoxetine was incubated with activated sludge inoculum (sludge solids content of 2,5 g/l) under aerobic conditions at 22 ± 3ºC for 96 hours. Over the course of the study, approximately 23% of the applied radioactivity was transformed and 1,92% was evolved as $^{14}CO_2$. One degradation product accounted for 19% of the applied radioactivity. The calculated DT50 for atomoxetine in sewage sludge was 136 hours. (Study 1982.6153)

Simulation studies:

The degradation potential of radiolabeled atomoxetine was also investigated in two static, aerobic water-sediment systems over 100 days following the OECD 308 guideline. ^{14}C-Atomoxetine applied to overlying water partitioned rapidly to sediment such that within 3 days, less than 50% remained in the water phase. At the end of the study 75,5 to 84,1% of the applied radioactivity in the water-sediment system was identified as atomoxetine and no more than 12,8% of the applied radioactivity was unextractable from the sediment. Additionally, 0,3 to 0,9% of the applied radiolabel had evolved as $^{14}CO_2$ after 100 days. While numerous minor

degradation peaks were observed in the water sediment system, the calculated DT50 values of atomoxetine from the two water sediment systems were 289 and 630 days. (Study 1982.6270)

Abiotic Degradation

Hydrolysis:

In a hydrolysis study (based on OECD guideline 111), atomoxetine degraded less than 10% when incubated at pH 4, 7, and 9 for 5 days at 50ºC. The DT50 at 25 ºC due to hydrolysis is estimated to be greater than 1 year. Atomoxetine has no significant ultraviolet absorption at wavelengths above 290 nm, and therefore is not expected to undergo substantial direct photolysis in aqueous solutions. (Study 1982.6151)

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 atomoxetine. Since the calculated DT50 values for two different systems were greater than 120 days, atomoxetine is considered to be potentially persistent.

Bioaccumulation

Partitioning coefficient:

The octanol/water partition coefficient of atomoxetine was determined using a shake flask method (based on OECD guideline 107). The log K_{ow} of atomoxetine at pH 4, 7, and 9 was determined to be 0,104; 0,676; and 2,81; respectively. (Study 1982.6149)

Justification of chosen bioaccumulation phrase:

Because the log K_{ow} is less than 4, atomoxetine has low potential to bioaccumulate in biotic tissues.

Excretion (metabolism)

Atomoxetine is subject to oxidative metabolism followed by conjugation. The major oxidative metabolite, 4-hydroxyatomoxetine, possesses similar activity and potency at the norepinephrine transporter as parent atomoxetine (see Strattera Package Insert). Because deconjugation reactions can occur in a sewage treatment facility and the major oxidative metabolite has pharmacological activity, no removal by human metabolism was used to calculate the PEC.

PBT/vPvB ASSESSMENT

Atomoxetine does not meet the REACH criteria for bioaccumulative or toxic (ECHA, 2017). Therefore, atomoxetine is not classified as PBT or vPvB.

References

ECHA, European Chemicals Agency. 2017. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT/vPvB Assessment and Chapter R.16: Environmental Exposure Estimation.

Strattera Package Insert. http://pi.lilly.com/us/strattera-pi.pdf

Strattera Capsules Safety Data Sheet. Revision 06/12/2017. http://ehs.lilly.com/msds/Strattera(Atomoxetine%20Hydrochloride).pdf

Study 1982.6149: Atomoxetine Hydrochloride - Determining the Partitioning Coefficient (n-Octanol/Water) of a Test Substance by the Flask-Shaking Method Following OECD Guideline 107 (August 2002).

Study 1982.6151: Atomoxetine Hydrochloride - Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECD Guideline 111 (August 2002).
Study 1982.6153: Atomoxetine Hydrochloride - Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test, Modified from OECD Guideline 302A (October 2002).
Study 1982.6270: [14C]Atomoxetine – Aerobic and Anaerobic Transformation in Aquatic Sediments Systems Following OECD Guideline 308 (May 2007).
Study 1982.6143: Atomoxetine Hydrochloride - Acute Toxicity to Water Fleas (Daphnia magna) Under Static Conditions, Following OECD Guideline #202 (August 2002).
Study 1982.6144: Atomoxetine Hydrochloride - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static-Renewal Conditions (August 2002).
Study 1982.6145: Atomoxetine hydrochloride - Acute Toxicity to the Freshwater Green Alga *Pseudokirchneriella subcapitata*, Following OECD Guideline #201 (August 2002).
Study 1982.6146: Atomoxetine Hydrochloride - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna,* Under Static Renewal Conditions, Following OECD Guideline #211 (August 2002).
Study 1982.6269: Atomoxetine HCl – Early Life-Stage Toxicity Test with Fathead Minnow, (*Pimephales promelas*), Following OECD Guideline #210 (May 2007).