FASS

Olanzapine Glenmark

Glenmark Pharmaceuticals Nordic

Tablett 7,5 mg

(gul, rund, platt, med avrundad kant, märkt "C" på ena sidan)

Neuroleptika

Aktiv substans:

Olanzapin

ATC-kod:

N05AH03

Läkemedel från Glenmark Pharmaceuticals Nordic omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för olanzapin är framtagen av företaget Lilly för Olansek, Olanzapin Lilly, Zyprexa®

Miljörisk: Användning av olanzapin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Olanzapin bryts ned i miljön.
Bioackumulering: Olanzapin 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 102,59 x 100

= 0,007 µg/l

Where:

A = 49,088 kg (total amount of olanzapine (free base) sold in Sweden in 2020, data from IQVIA). This number is not adjusted for metabolism

API form	kg/2020	kg olanzapin/2020
olanzapin	49,088	49,088
olanzapinembonatmonohydrat	7,5221352	7,5221352
Total Olanzapin		56,6101352

*calculated by multiplying by the molecular weight ratio of olanzapine free base:olanzapine pamoate monohydrate salt (312,4:718,83)

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*) (FDA 4.01) (Study J00394)
EC50 96 hr* (growth rate) > 14100 µg/l (highest concentration tested)
NOEC 14 d* (biomass) = 900 µg/l (based on mean concentration)
*although the study was conducted for 14 days, the growth rate was evaluated after 96 hours during the exponential growth phase

Crustacean (*Daphnia magna*)
Acute toxicity (FDA 4.08)
EC50 48 h (immobilization) = 8000 µg/l (Study C00295)
Chronic toxicity (OECD 211)
NOEC 21 days (survival, reproduction, growth) = 27 µg/l (Study 151A-110)

Rainbow trout (*Oncorhynchus mykiss*)
Acute toxicity (FDA 4.11)
LC50 96 h (mortality) = 1740 µg/l (Study F00595)

Fathead minnow (*Pimephales promelas*)
Chronic toxicity (OECD 210)
NOEC 5 d embryos + 28 d larvae (mortality, growth) = 11 µg/l (Study 151A-111B)

Calculation of PNEC

PNEC = 11 µg/l ÷ 10
PNEC = 1,1 µg/l
The PNEC was calculated from the NOEC for fathead minnows since 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 from three trophic levels: fish, daphnids and algae.

Environmental risk classification (PEC/PNEC Ratio)

PEC/PNEC = 0,007 ÷ 1,1 = 0,006

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

Degradation

Biotic Degradation

Inherent degradability:

When ^{14}C-olanzapine was aerobically incubated with activated sewage sludge, the half-life was 7,4 days (FDA 3.11). Several polar metabolites were observed over the 28-day study and 1,45% of the applied radioactivity evolved as $^{14}CO_2$. This study employed a concentration of sludge solids (40 mg/l) which is much lower than typical concentrations in a sewage treatment plant. (Study N00395)

Simulation studies:

Transformation of olanzapine was evaluated over 100 days in two static, aerobic water-sediment systems (OECD 308). ^{14}C-Olanzapine was applied to overlying water on Day 0 and by Day 14, no olanzapine was detected in water or sediment extracts and several transformation products were observed. The DT90 values for the disappearance of olanzapine from the two total water-sediment systems were both 2,6 days. In both systems, 4,2% of the applied radiolabel evolved as volatiles (mostly as $^{14}CO_2$). From Day 14 until the end of the study, the total amount of

radioactive residues in the sediment ranged from 76,7% to 95,5% of the applied radiolabel. From Day 14 until the end of the study, unextractable residues in the sediments ranged from 54,2% to 69,5% of the applied radiolabel. The extraction procedure from sediments (two extractions with methanol with 1% (v/v) ammonium hydroxide) was validated for olanzapine and was chosen from several methods using various organic solvents. (Study 151E-104)

Abiotic Degradation

Hydrolysis:

Olanzapine is hydrolytically stable. The DT50 values for olanzapine incubated at 25°C in aqueous buffers at pH 5, 7 and 9 ranged from 65 to 78 days. (Study N00195, FDA 3.09).

Justification of the degradation phrase:

Although there was evidence of biotransformation, the criteria for “inherently biodegradable” in activated sewage sludge was not met for olanzapine in study N00395. However, the half-life for olanzapine in water sediment systems was less than 32 days. Therefore, olanzapine is classified as degraded in the environment.

Bioaccumulation

Partitioning coefficient:

Log Kow = 0,3; 1,7; and 2,1 at pH values of 5, 7, and 9, respectively. (Study N00295, FDA 3.02)

Justification of chosen bioaccumulation phrase:

Because the log Kow is less than 4, olanzapine has a low potential for bioaccumulation.

Excretion (metabolism)

Olanzapine is extensively metabolized in humans to glucuronide conjugates of the parent and other oxidative products (Zyprexa Package Insert). Because deconjugation can occur in sewage treatment plants and oxidative products might have trace pharmacological activity, no removal by human metabolism was used to calculate the PEC.

PBT/vPvB ASSESSMENT

Olanzapine does not meet the criteria for persistent and bioaccumulative (ECHA 2017). Therefore, olanzapine 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.

Zyprexa Package Insert. http://pi.lilly.com/us/zyprexa-pi.pdf

Zyprexa® Tablets. Safety Data Sheet. Revision 02/09/2016. http://ehs.lilly.com/msds/ZyprexaTablets%20(Olanzapine).pdf

Study 151A-110. 2007. LY170053 – Full Life-Cycle Toxicity Test with Water Fleas (*Daphnia magna*) Under Flow-Through Conditions Following OECD Guideline #211.

Study 151A-111B. 2007. LY170053 – Early Life-Stage Toxicity Test with Fathead Minnow, (*Pimephales promelas*), following OECD Guideline #210.

Study 151E-103A. 2007. LY170053 – Activated Sludge Respiration Inhibition Test Following OECD Guideline 209.

Study 151E-104. 2007. [14-C]LY170053 – Aerobic and Anaerobic Transformation in Aquatic Sediment Systems Following OECD Guideline #308.

Study C00295. 1995. The 48-Hour Acute Toxicity of Olanzapine (LY170053) to *Daphnia magna* in a Static Test System.
Study F00595. 1995. The Acute Toxicity of Olanzapine (LY170053) to Rainbow Trout (*Oncorhynchus mykiss*) in a Static-Renewal Test System.
Study J00394. 1995. The 14-Day Acute Toxicity of Olanzapine (LY170053) to The Freshwater Green Alga (*Selenastrum capricornutum*) in a Static Test System.
Study N00195. 1995. A Study to Determine the Hydrolysis Rate of Olanzapine (LY170053) at 25°C at pH 5, 7, and 9.
Study N00295. 1995. A Study to Determine the Octanol/Water Partition Coefficient of Olanzapine at pH 5, 7, and 9.
Study N00395. 1995. A Study to Determine the Aerobic Biodegradation of ^{14}C-Olanzapine (LY170053) in Water Using a $^{14}CO_2$ Evolution Test Method.