FASS

Efient

M ℞ (F)

Lilly

Filmdragerad tablett 10 mg
(beige, sexkantig tablett, med prägling "10 MG" på ena sidan och "4759" på den andra)

Trombocytaggregationshämmande medel, exkl. heparin

Aktiv substans:
Prasugrel

ATC-kod:
B01AC22

Läkemedel från Lilly omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Prasugrel

Miljörisk: Användning av prasugrel har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Prasugrel bryts ned i miljön.
Bioackumulering: Prasugrel 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 1,399 x 100

= 0,0002 µg/l

Where:

A = 1,399 kg (total amount of prasugrel sold in Sweden in 2016 as prasugrel hydrochloride, data from QuintilesIMS). This number is not adjusted for metabolism.

API form	Sales in 2016 kg
prasugrelhydroklorid	1,53581652
prasugrel	1,399*

*calculated by multiplying the kg of prasugrel hydrochloride sold by the molecular weight ratio of prasugrel free base:prasugrel hydrochloride salt (373,442:409,90)

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 1982.6213)

EC50 72 hr (growth rate & biomass) > 1200 µg/l (highest concentration tested)
NOEC 72 hr (yield) = 250 µg/l

Crustacean (*Daphnia magna*)
Acute toxicity (OECD 202) (Study 1982.6210)
EC50 48 h (immobilization) > 2000 µg/l (highest concentration tested)
Chronic toxicity (OECD 211) (Study 1982.6223)
NOEC 21 days (survival, reproduction, growth) = 280 µg/l

Rainbow trout (*Oncorhynchus mykiss*)
Acute toxicity (OECD 203) (Study 1982.6211)
LC50 96 h (mortality) = 2100 µg/l

Fathead minnow (*Pimephales promelas*)
Chronic toxicity (OECD 210) (Study 1982.6224)
NOEC 5 d embryos + 28 d larvae (mortality, growth) = 190 µg/l

Calculation of PNEC
PNEC = 190 µg/l ÷ 10
PNEC = 19 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 = 0,0002 ÷ 19 = 0,00001

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

Degradation

Biotic Degradation

Inherent degradability:

When ^{14}C-prasugrel was aerobically incubated with activated sewage sludge (Study 1982.6271, based on OECD 302A), the radiolabeled compound was transformed rapidly such that prasugrel was not detected 15 minutes after initiation of incubation. The formation and degradation of several polar transformation products were observed. Additionally, there was formation of multiple very polar end-degradation products. The residues were subject to ultimate degradation as approximately 10% of the radiolabel was evolved as $^{14}CO_2$ over 28 days.

Simulation studies:

Transformation was studied in two water sediment systems in which radiolabelled prasugrel was incubated under aerobic conditions for 100 days (Study 1982.6289, based on OECD 308). Spiked sediment extraction methods (using acetonitrile, acetonitrile and water, and then acetonitrile, water and hydrochloric acid) were initially validated to recover 100% of the radioactivity from sediments and water. Additional solvent/water/acid extractions or solvent/water soxhlet extractions were used on sediments to ensure any further possible recovery of non-extractable residues during the middle and the end of the study. Results from the study demonstrated that parent prasugrel disappeared rapidly from the overlying water and sediments. After Day 0, the parent was not detected in the water and was 0,5% or

less in the sediment extracts. By the end of the study, 52 to 56% of the applied radioactivity was associated with the sediment and 45 to 47% of the applied radioactivity could not be extracted. Based on the non-extractable nature of these residues they were not considered to be prasugrel and were expected to be radioactive residues incorporated into the sediment matrix and not bioavailable. Of the radioactivity that could be extracted from sediment, the amount identified as prasugrel was ≤ 0,1% of the applied radioactivity. The calculated dissipation half-life values of prasugrel in the two water-sediment systems were 0,54 and 0,63 days. Several polar transformation products were observed in the water-sediment system; some of which were identified as metabolites that have been observed in mammalian species. As the study progressed, multiple very polar transformation end-degradation products were formed. No transformation product was more than 10% of the applied radioactivity by the end of the study. Additionally, 28 to 31% of the applied radioactivity was evolved as $^{14}CO_2$ by the end of the study.

Abiotic Degradation

Hydrolysis:

Prasugrel is subject to hydrolysis across the environmental pH range with the hydrolysis rate increasing with increasing pH (Study 1982.6208, based on OECD 111). The half-lives at 20°C at pH 4, 7, and 9 are 2,29 days, 0,83 days and 0,85 hours, respectively.

Justification of the degradation phrase:

Because the calculated DT50 values from the total water-sediment systems were less than one day and because the hydrolysis of prasugrel is rapid (2,29 days or less), prasugrel is considered to be degraded in the environment. In both the sludge and sediment

degradation studies, the primary degradation products were observed to undergo further degradation resulting eventually in mineralization or degradation to multiple very polar products that were likely incorporated into the organic matrices. Therefore, prasugrel was degraded in the environment.

Bioaccumulation

Partitioning coefficient:

Prasugrel is more water soluble at acidic pH values, with maximum aqueous solubility of 296, 2,61 and 1,29 mg/l at pH values of 4, 7, and 9, respectively (Study 1982.6207, based on OECD 105). As water solubility decreases with increasing pH, the measured K_{ow} increases. The log K_{ow} was measured to be 2,27, 3,80, and 5,66 at pH values of 4, 7, and 9, respectively (Study 1982.6226, based on OECD 107).

Justification of chosen bioaccumulation phrase:

Prasugrel is an ionic compound for which the measured log Kow increases over the environmental range. The measured log K_{ow} of prasugrel at pH 7 is less than 4 and, therefore, indicates that prasugrel is not expected to bioaccumulate in the environment. While log Kow is greater at higher pH values, prasugrel’s rapid degradation to more polar entities as well as its extensive metabolism to more polar metabolites, support the conclusion that prasugrel has low potential for bioaccumulation.

Excretion (metabolism)

Prasugrel is a thienopyridine prodrug that is rapidly de-esterified in humans to the inactive thiolactone. The thiolactone is metabolized to the active adenosine diphosphate receptor antagonist, which is

subsequently metabolized to inactive compounds. Like prasugrel, neither the thiolactone nor the active entity is excreted from humans. See Efient EPAR and Effient Package Insert.

PBT/vPvB ASSESSMENT

Prasugrel does not meet the REACH criteria for persistent, bioaccumulative or toxic (ECHA, 2017). Therefore, prasugrel 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 Assessment and Chapter R.16: Environmental Exposure Estimation.
Effient Package Insert. http://pi.lilly.com/us/effient.pdf
Efient EPAR.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Publ
Effient Safety Data Sheet. Revision 09/23/2015.
http://ehs.lilly.com/Efient Safety Data Sheet/Effient.pdf
Study 1982.6207: LY640315 HCl - Determination of the Water Solubility of a Test Substance Following OECD Guideline 105 (2005).
Study 1982.6226: LY640315 HCl - Determining the Partitioning Coefficient (n-Octanol/Water) of a Test Substance by the Flask-Shaking Method Following OECD Guideline 107 (2006).
Study 1982.6208: [^{14}C]LY640315 - Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECD Guideline 111 (2004).
Study 1982.6271: LY640315 – Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test Using Radiolabelled Test Material, Modified from OECD Guideline 302A (2007).

Study 1982.6212: LY640315 HCl - Acute Toxicity to the Freshwater Green Alga Pseudokirchneriella subcapitata, Following OECD Guideline #201 (2005).
Study 1982.6210: LY640315 HCl - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Flow-Through Conditions, Following OECD Guideline #202 (2005).
Study 1982.6211: LY640315 HCl - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Conditions, Following OECD Guideline 203 (2005).
Study 1982.6223: LY640315 HCl – Full Life-Cycle Toxicity Test with Water Fleas (*Daphnia magna*) Under Flow-Through Conditions, Following OECD Guideline #211 (2005).
Study 1982.6224: LY640315 HCl – Early Life-Cycle Toxicity Test with Fathead Minnow, (Pimephales promelas), Following OECD Guideline #210 (2005).