FASS

Tasigna

Novartis

Kapsel, hård 50 mg

(De hårda kapslarna är röda/ljusgula. Varje hård kapsel är präglad i svart (”NVR/ABL”).)

Antineoplastiska medel, proteinkinashämmare

Aktiv substans:

Nilotinib

ATC-kod:

L01EA03

Läkemedel från Novartis omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Nilotinib

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

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100)$ = $1.37*10^{-6}$ * A * (100 - R) = $1.37*10^{-6}$ * 43.2354 kg * 100 = 0.005923 µg/L = 5.9232 ng/L

Where:
A = 43.2354 kg (total sold amount API in Sweden year 2022, data from IQVIA).
R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0, if no data is available.
P = number of inhabitants in Sweden = $10 * 10^{6}$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Pseudokirchneriella subcapitata) (OECD 201) (Harlan Laboratories Study C97316)*:*
ErC50 96 h (growth rate) > 4.7 µg/L
NOEC ≥ 4.7 µg/L, Maximum testing concentration due to the water solubility limit of the test item. Not toxic up to the limit of water solubility of the test item.

Crustacean (Daphnia magna):
Acute toxicity
EC50 48 h (immobilization) > 100.0 mg/L Nominal concentration; not toxic up to the limit of water solubility (92/69/EC (L383) C.2) (ARC Study No.: NOV255)
Chronic toxicity
NOEC 21 days (survival and reproduction) ≥ 0.0127 mg/L. Maximum testing concentration due to the water solubility limit of the test item. Not toxic up to the limit of water solubility. (OECD 211) (RCC Study No. A94083)

Fish (Danio rerio, zebrafish)*:*
Acute toxicity
LC50 96 h (lethality) > 100.0 mg/L (96h, 92/69/EEC (L383) C1) (ARC Study No.: NOV256)
Chronic toxicity
NOEC 35 days (hatching rate, survival of larvae and juvenile fish, fish length and weight) ≥ 0.013 mg/L. Maximum testing concentration due to the water solubility limit of the test item. Not toxic up to the limit of water solubility. (OECD 210) (Harlan Laboratories Study No. C97327)
NOEC 7 days (egg development and hatching rate) = 0.0026 mg/L (OECD212 / OECD210) (RCC Study A94138)

Other ecotoxicity data:
Bacterial respiration inhibition
EC_{50} 3 h > 300.0 mg/L (activated sludge respiration inhibition) (87/302/EEC, Part C) (ARC Study No.: NOV257)
Sediment-dwelling organisms (*Chironomus riparius*, non-biting midge)
NOEC 27 days (emergence and development rate) ≥ 0.0174 mg/L (OECD 219) (RCC Study No. A94116)

PNEC derivation:
PNEC = 0.26 µg/L
The PNEC (µg/L) is based on the lowest NOEC/10, where 10 is the assessment factor used if chronic data for 3 trophic levels is available. The NOEC for the 7 day zebra fish study has been used for this calculation since it is the most sensitive of the three tested species.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.0059 µg/L / 0.26 µg/L = 0.022, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of nilotinib has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:
22.3 % degradation in 28 days; not readily degradable (92/69/EC (L383) C.4-C). (ARC Study No.: NOV258)
Simulation studies:

DT50 (total system) = 84.0 – 100.0 days
DT50 (water phase) = 0.4 – 0.6 days (OECD 308) (Harlan Laboratories Study C97250)
The water and sediment phases were separated and the sediment was exhaustively extracted with acetonitrile/water (4:1; v/v). Soxhlet extraction using acetonitrile/water (4:1; v/v) was additionally performed on the extracted sediments from day 1 onwards. The sediment samples from the 100-day interval were submitted to acidic reflux extraction using acetonitrile/0.1 M HCl (1:1; v/v).
Nilotinib dissipated rapidly from the water phases of both aquatic systems due to adsorption to the sediment. Immediately after application, its concentration in the water phase represented on average 91.9% (river) and 92.4% (pond) of the applied radioactivity decreasing to 1.2% and 4.6% of applied after 7 days. From day 14 (river) and day 28 (pond) onwards, the amounts of applied radioactivity were below 2% in the water phases of both systems. The level of the parent substance in the sediments increased to maximum levels of 46.0% (river) and 40.6% (pond) of applied radioactivity on day 100; thereafter it declined to 25.5% (river) and 19.9% (pond) of applied radioactivity by the end of the study. The amount of nilotinib declined from initial levels of 91.9% (river) and 92.4% (pond) of the applied radioactivity to 25.5% and 19.9% by the end of the study (day 128).

Justification of chosen degradation phrase:
Nilotinib is not readily biodegradable. Based on the DT50 for the total system, the phrase 'Nilotinb is slowly degraded in the environment' is chosen.

Bioaccumulation

Bioconcentration factor (BCF):
Steady state Biological Concentration Factor (BCF_{ss}) = 65 - 75
Lipid content normalised BCF (BCF_{L}) = 107 - 127 (OECD 305; 28 days; Rainbow trout (*Oncorhynchus mykiss*)). (Harlan Laboratories Study C97261)
Partitioning coefficient:
Log Dow = 3.6 at pH 7, 30°C (92/69/EC (L383) A.8). (Study NOV253E)
Justification of chosen bioaccumulation phrase:
Since BCF < 500, nilotinib has low potential for bioaccumulation.

Excretion (metabolism)

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in feces. Parent drug accounted for 69% of the dose. (Novartis Core Data Sheet, Tasigna® 2016).

References

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
- Harlan Laboratories Study C97316. Final report: 30. May 2011
- ARC Study No.: NOV255. Final report: 02. August 2005
- RCC study No. A94083. Final Report: 29 January 2007.
- ARC Study No.: NOV256. Final report: 02 August 2005.
- Harlan Laboratories Study C97327. Final Report: 07. June 2011.
- RCC study number: A94138. Final report: 01. February 2007
- ARC Study No.: NOV257. Final report: 06 June 2005.
- RCC study number: A94116. Final report: 07. February 2007

- ARC Study No.: NOV258. Final report: 06 June 2005
- Harlan Laboratories Study C97250. Final report: 26 May 2011.
- Harlan Laboratories Study C97261. Final report: 11. January 2011.
- Study NOV253E. Final report: 02. June 2005
- Tasigna®(nilotinib), Novartis Cores data sheet, Version 1.8. 05 December 2016