FASS

Nexavar

MRF

Bayer

Filmdragerad tablett 200 mg
(röd, rund, fasetterad bikonvex filmdragerad tablett, märkt med Bayerkors på ena sidan och "200" på den andra)

Proteinkinashämmare

Aktiv substans:
Sorafenib

ATC-kod:
L01EX02

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

Miljöpåverkan

Sorafenib

Miljörisk: Särskilt miljöfarliga egenskaper
PBT/vPvB-klass: I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans

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) = 0.0017 µg/L

Where:

A = 12.43 kg (total sold amount API in Sweden year 2021, data from IQVIA / LIF)

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) (Reference I)

D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Reference I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Algae (*green algae*, Desmodesmus subspicatus):*

NOEC 72 h (growth rate) ≥ 0.536 µg/L, E_rC_{50} 72 h (growth rate) > 0.536 µg/L. Guideline OECD 201. (Reference II)

*Crustacean (*waterflea, *Daphnia magna):*

Chronic toxicity

NOEC 21 days (reproduction) ≥ 0.86 µg/L. Guideline OECD 211. (Reference III)

*Fish (*fathead minnow, *Pimephales promelas):*

Chronic toxicity

EC_{10} 28 days (survival) = 0.17 µg/L. Guideline OECD 210.

(Reference IV)

The PNEC was calculated by division of the NOEC of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group were fish and the lowest NOEC was reported as 0.17 µg/L. The regulatory default standard AF of 10 was used, which is applicable when there are chronic aquatic toxicity studies representing the three trophic levels (algae, crustaceans, and fish).
PNEC = 0.17 µg/L / 10 = 0.017 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.0017 µg/L / 0.017 µg/L = 0.1.

Justification of chosen environmental risk phrase:
With a risk quotient ≤ 0.1 sorafenib tosylate qualifies for the phrase “Use of sorafenib tosylate has been considered to result in insignificant environmental risk.”
However, sorafenib tosylate was determined to be a PBT substance (see below) and therefore, the appropriate risk phrase is “Hazardous environmental properties”.

Degradation

Biotic degradation

Ready degradability:
Biodegradation of sorafenib tosylate was determined in an OECD 301F study. 200 mg/L as ThOD were introduced in the test system

using municipal sewage sludge. The reference substance (sodium diacetate) was degraded to more than 60 % within 14 days and the toxicity control did not indicate an inhibiting effect on microorganisms.
The study reported 0 % biodegradation in 28 days. Guideline OECD 301F. (Reference V)

Simulation studies:

In an OECD 308 study the transformation of [^{14}C] sorafenib tosylate in sediments and natural water was assessed in two different aerobic sediment/water systems at a temperature of 19-23 °C for 114 days, continuously in the dark.

Radioactivity of [^{14}C] sorafenib tosylate in sediment was quantified by combustion analysis and radio-assay. The water fraction was measured by liquid scintillation counting (LSC). Hydrochloric acid was added to the soda lime fraction and evolving $^{14}CO_2$ was absorbed in a scintillation cocktail and analysed by LSC. Samples for analyses were taken after 2, 15, 29, 43, 64 and 114 days. Three test vessels for each time point were removed for analysis.

The distribution of [^{14}C] sorafenib tosylate to the sediment compartment and the disappearance from the water fraction was determined by plotting the radioactivity over time. The disappearance time (DT_{50}) was calculated by a kinetic modelling software (KIM). The half-lifes of [^{14}C] sorafenib tosylate were 0.5 and 0.6 days for Nordhafen (higher organic carbon content) and Tegeler See (lower organic carbon content), respectively, in the overlying water.

Only 0.3 and 0.4 % of the applied radioactivity evolved as $^{14}CO_2$ and therefore, no half-life for overall disappearance was calculated.

The total mass balance accumulated to 98.2 and 99.9 % for Tegeler See and Nordhafen, respectively (day 29). Towards the end of the incubation period, only 74.0 and 75.4 % of the total radioactivity was recovered. This is most likely due to the binding of test material to the glass surface of the test vessels.
This study reported a half-life of substance sorafenib tosylate in water DT_{50} = 0.5-0.6 days while no DT_{50} could be derived for sediment/total system. Guideline OECD 308. (Reference VI)

Abiotic degradation

Justification of chosen degradation phrase:
Sorafenib tosylate was not (readily) biodegradable, which qualifies for the phrase “Sorafenib tosylate is potentially persistent”.

Bioaccumulation

Bioconcentration factor (BCF):
The bioaccumulation potential of sorafenib tosylate was determined in an OECD 305 study with *Lepomis macrochirus*. The fish were exposed for 26 days at 0.1 and 1 µg/L of the test item (uptake phase), followed by the depuration phase of 16 days.
The test substance was administered as [^{14}C] labelled sorafenib. Fish and water were sampled during the uptake and the depuration phase. Water was directly measured in a liquid scintillation counter, while fish were decomposed in soluol, a strongly oxidizing compound. The solution was then also analyzed by liquid scintillation counting.
The calculated BCF at steady state conditions was 5300 at 1 µg/L. At 0.1 µg/L, no steady state was reached, however, at the end of the exposure phase the BCF calculated as 7250.

The study reported a BCF range of 5300-7250. Following temperature correction to 12 °C the range is 17032-23298. Guideline OECD 305. (Reference VII)

Partitioning coefficient:

The log D_{ow} was reported as 3.7 at pH 7. Guideline OECD 117. (Reference VIII)

Justification of chosen bioaccumulation phrase:

Due to the BCF > 500 sorafenib tosylate is considered bioaccumulative which qualifies for the phrase “Sorafenib tosylate has high potential for bioaccumulation”.

PBT/vPvB assessment

According to the established EU criteria, sorafenib tosylate should be regarded as a PBT/vPvB substance as a) the substance is neither readily biodegradable nor could half-lives be determined and hence it is considered persistent, b) the bioaccumulation factor ranged between 17,032-23,298 and exceeds the threshold of 5000, and c) the lowest NOEC of 0.17 µg/L falls short of the threshold of 10 µg/L.

References

I. Guidance on information requirements and Chemical Safety Assessment Chapter R.16: Environmental exposure assessment. V3.0, Feb. 2016.
II. Growth inhibition test of Sorafenibtosylate (BAY 54-9085) on the green algae Desmodesmus subspicatus. Bayer Schering Pharma AG, Berlin, Nonclinical Drug Safety. Report no. A42279, study no. TOXT2078665.

III. Reproduction study of sorafenibtosylate (BAY 54-9085) in Daphnia magna. Bayer Schering Pharma AG, Berlin, Nonclinical Drug Safety. Report no. A42837, study no. TOXT3079089.

IV. Early-life-stage test with sorafenibtosylate (Bay 54-9085) on the fathead minnow (Pimephales promelas). Bayer Schering Pharma AG, Berlin, Nonclinical Drug Safety. Report no. A44229, study no. TOXT5079595.

V. Study on the biodegradability of Sorafenibtosylate (BAY 54-9085) in the manometric respiration test. Bayer Schering Pharma AG, Berlin, Nonclinical Drug Safety. Report no. A41886, study no. T8078913EXT/1121.002.760.

VI. Aquatic-sediment study (aerobic) with [14C] sorafenibtosylate ([14C]BAY 54-9085). Bayer Schering Pharma AG, Berlin. Report no. A42733, study no. TOXT9078635.

VII. Bioaccumulation study of sorafenib in fish (Lepomis machrochirus). Bayer Schering Pharma AG, Berlin, Nonclinical Drug Safety. Report no. A51426, study no. TOXT7082142.

VIII. Sorafenib tosylate/ BAY54-5985/Report on physicochemical properties/Partition coefficient octanol-water (HPLC method). Bayer Schering Pharma AG, Berlin, Analytical Development Physical Chemistry. Report no. A44552, study no. TOXT9078635.