FASS

GIOTRIF

Boehringer Ingelheim

Filmdragerad tablett 30 mg

(Mörkblå, runda, bikonvexa, avfasade, filmdragerade, präglade med koden”T30” på ena sidan och Boehringer Ingelheim företagssymbol på andra sidan. 9,1 x 9,1 mm.)

Antineoplastiska medel, proteinkinashämmare

Aktiv substans:
Afatinib

ATC-kod:
L01EB03

Läkemedel från Boehringer Ingelheim omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Afatinib

Miljörisk: Användning av afatinib har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Afatinib bryts ned i miljön.
Bioackumulering: Afatinib 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) = $(A*10^{9}*(100-R))/ (365*P*V*D*100) = 1.5*10^{-6}*A (100-R) = 4.8*10^{-5}$ µg/L

Where:
A = 0.35 kg (total sold amount API in Sweden year 2020, data from IQVIA).
R = 0 % removal rate.
P = number of inhabitants in Sweden = $10*10^{6}$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (I)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (I)

Predicted No Effect Concentration (PNEC)
PNEC = 3.2 µg/L

The PNEC has been derived from the lowest NOEC (Zebra fish, 35d) of 32 ug/L. An assessment factor of 10 is used based on the availability of a NOEC for algal growth inhibition in combination with chronic toxicity studies for the other two trophic levels in accordance with ECHA Guidelines (I).

Ecotoxicological studies
Algae (Pseudokirchneriella subcapitata)(OECD 201) (II)
72-hour EC50 (biomass) = 8.6 mg/L
72-hours NOEC (biomass) = 1.2 mg/L

72-hour EC50 (growth rate) = 33 mg/L
72-hours NOEC (growth rate) = 1.2 mg/L

Water-flea (Daphnia magna) (OECD 211) (III)
21-day NOEC: 2.7 mg/L
21-day LOEC: 8.9 mg/L

Zebra fish (Brachydanio rerio) (OECD 210) (IV)
35-day NOEC: 0.032 mg/L

Environmental risk classification (PEC/PNEC ratio)
PEC/PNEC = $4.8*10^{-5}$ (µg/L) / 3.2 (µg/L) = $1.5*10^{-5}$, i.e. PEC/PNEC < 0.1 which justifies the phrase; "Use of Afatinib has been considered to result in insignificant environmental risk".

Degradation
Biotic degradation
Ready biodegradability: Not ready biodegradable
0% in 28 days (OECD 301B). (V)

Simulation studies:
The following dissipation rates (DT50) for Afatinib in a river (r) and pond (p) system, respectively, were determined in a OECD 308 study (VI):

- Freshwater: 0.8 days (r) and 1.1 days (p).

Sediment: Since the dissipation half lives in the sediment phase were not reached within the experimental time frame, no kinetic evaluation was performed.

- Total system: 6.8 days (r) and 2.3 days (p).

At the end of the study (day 99), 0.3% (r) and 0.4% (p) of applied radioactivity was remaining as parent compound in the total river and pond system, respectively. The amount of non-extracted radioactivity continuously increased with time. Non-extracted residues accounted for 7.0% and 6.3% of applied radioactivity on time 0 and increased to levels of 48.1% and 62.5% of applied at day 99 in the river and pond sediments, respectively.
After removing the water phase from the test system, the sediment was submitted to up to four extraction steps using acetonitrile/water (4:1; v/v) or acetonitrile/water (4:1; v/v) at pH 3 at room temperature

(Ambient extracts). These extractions at room temperature were performed in a shaker at about 200-250 strokes per minute each for about 30 minutes. The amount of solvent used was in general about 1 mL/g sediment (wet weight basis). For interval 1 day, one extraction step was performed using methanol/water (4:1, v/v) at pH 3. Except for time 0, two hot reflux extraction steps using acetonitrile/water (4:1; v/v) at pH 3 for 4 hours were additionally performed on the extracted sediment samples. The latter method is considered as a harsh extraction. It was performed rather to enhance extraction efficiency for analytical purposes, than to determine the bioavailable residue fraction. The radioactivity in the individual extracts was quantified by LSC. If necessary, the extracts and combined extracts were then concentrated under a stream of nitrogen at about 35 °C. The concentrated extracts were re-dissolved in acetonitrile/water and submitted to chromatographic analysis (HPLC).
The largest unknown component in the sediment extracts was identified to correspond to the reference item R1
(1-4-(3-Chloro-4-fluoro-phenylamino)-7-((S)-(tetrahydrofuran-3-yl)oxy)-quinazolin-6-yl)-5-hydroxy-pyrrolidon-2-or
CD 334 XX). It accounted for up to 10% and 11% of applied in the river and pond system on day 28. The other transformation products did individually not exceed mean values of 5.0% of the applied radioactivity in either system. The mineralization of the test item and the formation of other organic volatiles were insignificant, accounting for not more than 0.2% and 0.1% of the applied radioactivity for both systems during the 99 days of incubation.

In conclusion, Afatinib rapidly dissipates from the water phase by adsorption to the sediment. Once in the sediment, its degradation proceeds at a slower rate, mainly via hydrolysis to the reference item R1 or the formation of non-extracted residues.

Abiotic degradation
Hydrolysis:
At pH 4: 6% degradation after 8 weeks at 25 ºC
At pH 7: 37% degradation after 8 weeks at 25 ºC (VII)

Justification of the chosen degradation phrase:
Afatinib does not pass the ready degradation test but is degraded in sediment where the total system DT50 ≤ 32d and less than 15% remains as the parent compound at the end of the study. Abiotic degradation through hydrolysis is slow. Considering all data, the phrase “Afatinib is degraded in the environment” is assessed as most relevant.

Bioaccumulation
Bioconcentration factor (BCF_{fish}):

- High dose level: 9.7
- Low dose level: 9.2 (OECD 305). (VIII)

Partitioning coefficient:

- Log D_{ow} = 3.68 at pH 7.

Justification of the chosen bioaccumulation phrase:
Since BCF < 500, Afatinib has low potential for bioaccumulation.

Excretion (metabolism)
Afatinib is excreted to 64% as parent compound. The pharmacological activity of the metabolites is not known. (IX)

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
II. Study report (U10-0065-01) , 2010
III. Study report (U10-0064-01) , 2010
IV. Study report (U10-0064-01), 2010
V. Study report (U09-0246-01), 2009
VI. Study report (U10-1923-01), 2010
VII. Study report (U03-1776-02), 2009
VIII. Study report (U10-0058-01), 2010
IX. Study report (U10-2883-01), 2010