FASS

Inlyta®

Pfizer

Filmdragerad tablett 1 mg
(Röd oval filmdragerad tablett med "Pfizer"präglat på den ena sidan och "1 XNB" på den andra.)

Antineoplastiska medel, proteinkinashämmare

Aktiv substans:
Axitinib

ATC-kod:
L01EK01

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

Miljöpåverkan

Axitinib

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

Detaljerad miljöinformation

Biodegradation studies conducted in sludge indicate axitinib will undergo some degradation during the wastewater treatment process. Based on a sludge sorption coefficient (K_d) of 1491, an estimated 19.7% of axitinib will be removed through sorption to sludge during the wastewater treatment process. Upon release of wastewater effluents into the aquatic environment, axitinib residues will reside in the water and sediment compartments. Based on an aqueous dissipation half-life of 3.7 – 6.0 days, axitinib is expected to dissipate from the water to the sediment. Multiple degradation products, all present at <10%, were observed in sediment extracts therefore, axitinib is expected to continue to degrade in the sediment compartment. Total water-sediment system half-life values were 110 and 112 days.

Physical properties[4]

Solubility at pH 5.2-7.8: 200 µg/L
pKa: 4.2
Vapor pressure: $<1\times10^{-7}$ mmHg

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$PEC\ (\mu g/L) = (A\times10^{9}\times(100-R))/(365\times P\times V\times D\times100) = 1.37\times10^{-6}\times A(100-R)$

PEC = 1.31×10^{-5} µg/L

Where:

A =	0.118664 kg (total sold amount API in Sweden year 2021)[3]
R =	19.7% removal rate (due to loss by adsorption to sludge particles as calculated in the OECD 106 study)[11]
P =	number of inhabitants in Sweden = 10×10^{6}
V (L/day) =	wastewater volume per capita and day = 200 (ECHA default)[1]
D =	factor for waste water dilution by surface water flow = 10 (ECHA default)[1]

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green alga (Raphidocelis subcapitata) (guideline OECD 201)[5]

EC_{50} 72 h (biomass, chronic toxicity) = 900 µg/L

NOEC 72 h (biomass, chronic toxicity) = 430 µg/L

EC_{50} 72 h (growth rate, chronic toxicity) = >1500 µg/L

NOEC 72 h (growth rate, chronic toxicity) = 430 µg/L

Daphnids (Daphnia magna) (guideline OECD 211)[6]
NOEC 21 days (reproduction, chronic toxicity) = 88 µg/L

Fathead Minnow (Pimephales promelas) (guideline OECD 210)[7]
LOEC 32 days (reproduction, chronic toxicity) = 7.2 µg/L
NOEC 32 days (reproduction, chronic toxicity) = 3.5 µg/L

Midge (Chironomus riparius) (guideline OECD 218)[8]
LOEC 28 days (emergence, chronic toxicity) = >100 000 µg/kg
NOEC 28 days (emergence, chronic toxicity) = 100 000 µg/kg

Activated sludge microorgansims (guideline OECD 209)[12]
EC_{15} (respiration inhibition) = 737 000 µg/L
EC_{50} (respiration inhibition) = >1000 000 µg/L

Based on the lowest NOEC for the species *Pimephales promelas* and using the assessment factor[2] of 10, the PNEC is calculated to 3.5/10 = 0.35 µg/L.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 1.31×10^{-5} / 0.35 = 3.73×10^{-5}, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase ”Use of axitinib has been considered to result in insignificant environmental risk”.

Adsorption (guideline OECD 106)[11]

Solid	K_d (L/Kg)	K_{oc} (L/Kg)

Activated sludge	1491	4626
HOM soil (Don Ulgem)	2113	5333
LOM soil (Speyer)	128	367
HOM sediment (Tauton)	3670	5679
LOM sediment (Weweantic)	87	267

HOM = high organic matter, LOM = low organic matter

Using the formula $(0.165 \times K_d) / [(0.165 \times K_d) + 1000]$ where 0.165 represents the grams of sludge wasted per 1000 grams of wastewater treatment plants' aqueous effluent, we can estimate the fraction of the substance removed onto sludge solids during wastewater treatment. Based on the sludge K_d of 1491, the fraction of the substance estimated to be removed on wasted sludge is: $(0.165 \times 1491) / [(0.165 \times 1491) + 1000)] = 0.197$ or 19.7%.

Degradation

Biotic degradation

Simulation studies (guideline OECD 308)[9]

A 102 day study was conducted to evaluate the degradability of the parent substance in two different river water-sediment systems, Taunton River (high organic content) and Weweantic River (low organic content) sediments. Extraction of the parent substance from the sediment was performed once with acetonitrile (200 mL) and up to two additional times with acetonitrile:purified reagent water: trifluoroacetic acid (80:20:0.1, v:v:v, 150 mL). Additional

extractions were performed on day 102 sediments using methanol:water:hydrochloric acid (3 times), then once with ethyl actate and once with hexane.

The results from the study are shown in the table below.

Data on day 102	Taunton River	Weweantic River
Total System		
Half-life (days)	100	112
Total $^{14}CO2$ (% of radioactivity)	0.8	0.6
Aerobic Water Layer		
Half-life (days)	6.0	3.7
Axitinib (% of radioactivity)	ND	ND
Sediment Fraction		
Bound (% of radioactivity)	46.1	25.9
Extractables (% of radioactivity)	46.5	72.8
Axitinib (% of radioactivity)	43.3	50.3

ND = not detected

WWTP degradation (guideline OECD 314B)[10]

The 28-day study was conducted to evaluate the rate and extent of primary biodegradation and mineralization of the test substance in activated sludge, i.e. an estimation on the removal of axitinib from wastewater. The data from the study is shown below.

Parent compound remaining at the end of the study: 4.7%
Total mineralisation: 3.4%
Total system DT_{50}: 4.2 days

Justification of chosen degradation phrase
As the highest total system DT_{50} value (water-sediment simulation study, OECD 308) was calculated to 112 days, it corresponds to the degradation phrase ”The substance is slowly degraded in the environment”.

Bioaccumulation

Partitioning coefficient (guideline OECD 107)[13]
Log D = 2.19 at pH 4
Log D = 2.01 at pH 7
Log D = 1.94 at pH 9

Justification of chosen bioaccumulation phrase
Since log D_{ow} < 4 at pH 7, the substance has low potential for bioaccumulation.

References

1. ECHA, European Chemicals Agency. 2016 Guidance on information requirements and chemical safety assessment chapter R16.
2. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment chapter R10.

3. IQVIA KG Consumption 2021 report.
4. Axitinib environmental risk assessment. February 2011.
5. Study report 2438.6627: Axitinib – 72-hour acute toxicity test with freshwater green alga, *Pseudokirchneriella subcapitata,* following OECD guideline 201. February 2011.
6. Study report 2438.6628: Axitinib – Full life-cycle toxicity test with water fleas, *Daphnia magna*, under flow-through conditions, following OECD guideline #211. February 2011.
7. Study report 2438.6629: Axitinib – Early life-stage toxicity test with fathead minnow, *Pimephales promelas*, following OECD guideline #210. January 2011.
8. Study report 2438.6661: Axitinib – Toxicity test with sediment-dwelling medges (*Chironomus riparius*) under static conditions, following OECD guideline 218. September 2011.
9. Study report 2438.6633: Axitinib - Aerobic transformation in aquatic sediment systems following OECD guideline 308. December 2010.
10. Study report 2438.6631: [^{14}C]Axitinib – Determination of the biodegradability of a test substance in activated sludge based on OECD guideline 314B. December 2010.
11. Study report 2438.6626: [^{14}C] Axitinib – Determining the adsorption coefficient (K_{oc}) following OECD guideline 106. December 2010.
12. Study report 2438.6630: Axitinib – Determination of activated sludge respiration inhibition test following OECD guideline 209. December 2010.
13. Study report 2438.6625: [^{14}C] Axitinib – Determining the partitioning coefficient (n-octanol/water) by the flask-shaking method following OECD guideline 107. December 2010.