

## Inlyta<sup>®</sup>

M R F

**Pfizer**

Filmdragerad tablett 3 mg

(Röd rund filmdragerad tablett med Pfizer präglat på den ena sidan och 3 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<sup>4</sup>

Solubility at pH 5.2-7.8: 200 µg/L

pKa: 4.2

Vapor pressure:  $<1 \times 10^{-7}$  mmHg

### Environmental Risk Classification

#### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \times 10^9 \times (100 - R)) / (365 \times P \times V \times D \times 100) = 1.37 \times 10^{-6} \times A(100 - R)$$

$$PEC = 1.31 \times 10^{-5} \mu\text{g/L}$$

Where:

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

### Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Green alga (Raphidocelis subcapitata) (guideline OECD 201)*<sup>5</sup>

EC<sub>50</sub> 72 h (biomass, chronic toxicity) = 900 µg/L

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

EC<sub>50</sub> 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)*<sup>6</sup>

NOEC 21 days (reproduction, chronic toxicity) = 88 µg/L

*Fathead Minnow (Pimephales promelas) (guideline OECD 210)*<sup>7</sup>

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)*<sup>8</sup>

LOEC 28 days (emergence, chronic toxicity) = >100 000 µg/kg

NOEC 28 days (emergence, chronic toxicity) = 100 000 µg/kg

*Activated sludge microorganisms (guideline OECD 209)*<sup>12</sup>

EC<sub>15</sub> (respiration inhibition) = 737 000 µg/L

EC<sub>50</sub> (respiration inhibition) = >1000 000 µg/L

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

Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 1.31 \times 10^{-5} / 0.35 = 3.73 \times 10^{-5}$ , i.e.  $PEC/PNEC \leq 0.1$

which justifies the phrase "Use of axitinib has been considered to result in insignificant environmental risk".

**Adsorption (guideline OECD 106)**<sup>11</sup>

Solid	K <sub>d</sub> (L/Kg)	K <sub>oc</sub> (L/Kg)
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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)<sup>9</sup>*

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 acetate and once with hexane.

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

<b>Data on day 102</b>	<b>Taunton River</b>	<b>Weweantic River</b>
<i><b>Total System</b></i>		
Half-life (days)	100	112
Total <sup>14</sup> CO <sub>2</sub> (% of radioactivity)	0.8	0.6
<i><b>Aerobic Water Layer</b></i>		
Half-life (days)	6.0	3.7
Axitinib (% of radioactivity)	ND	ND
<i><b>Sediment Fraction</b></i>		
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)<sup>10</sup>*

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)<sup>13</sup>*

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.
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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.
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9. Study report 2438.6633: Axitinib - Aerobic transformation in aquatic sediment systems following OECD guideline 308. December 2010.
10. Study report 2438.6631: [<sup>14</sup>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: [<sup>14</sup>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: [<sup>14</sup>C] Axitinib – Determining the partitioning coefficient (n-octanol/water) by the flask-shaking method following OECD guideline 107. December 2010.