

## **Environmental Risk Assessment Summary**

### **Alectinib**

#### **Introduction**

The publication of environmental risk assessment summaries is part of Roche's engagement on developing a better understanding of issues regarding pharmaceuticals in the environment (PiE).

New pharmaceutical substances are investigated for biodegradability and initial ecotoxicity during their development. For registration, a full state-of-the-art environmental risk assessment is developed based on chronic environmental effects and advanced environmental fate data, as required by the pertinent regulations. While not a regulatory requirement, Roche also investigates older pharmaceutical substances, normally at a simpler scale, in order to assess their environmental risks.

For active pharmaceutical ingredients, the potential environmental risk is calculated from the ratio between the predicted environmental concentration (PEC) of the substance in the aquatic environment based on a conservative emission scenario and the predicted no effect concentration (PNEC), a concentration below which no adverse effects on the environment have to be expected.

#### **Summary**

Alectinib is an oral medicine, used for the treatment of people with non-small cell lung cancer (NSCLC) whose tumours are identified as anaplastic lymphoma kinase (ALK)-positive. Alectinib is a tyrosine kinase inhibitor that targets ALK fusion proteins, preventing signalling within cancer cells to inhibit their growth and survival [12].

Alectinib is the active pharmaceutical ingredient used in the Roche product Alecensa.

Preliminary studies indicated that predominantly Cytochrome P450 3A4 (CYP3A4) mediated the Alectinib metabolism. Alectinib is eliminated from human plasma in with a median apparent terminal  $t_{1/2}$  ranging from 18.2 to 25.3 hours. In mass-balance studies, Alectinib was excreted predominantly by faecal pathway [12].

Alectinib is not readily biodegradable in standard OECD tests over 28 days. In water/sediment systems over 102 days, partial transformation of Alectinib was observed. No mineralisation (formation of CO<sub>2</sub>) was observed.

The PEC/PNEC ratio is 0.00002. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [11], a PEC/PNEC ratio of <1 means that Alectinib and/or its metabolites are unlikely to represent a risk to the aquatic environment.

### Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

$$\text{PEC (ng/L)} = (A \times 10^9 \times (1-R)) \div (365 \times P \times V \times D)$$

- A Total patient consumption of Alectinib in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [16])
- R Removal rate during sewage treatment = 0.68 (68% as calculated by the fate and emission prediction model SimpleTreat 4.0 [18])
- P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [13]; resulting in a consumption of 0.6 mg/inhabitant
- V Volume of wastewater per inhabitant and day (default value) = 200 L day<sup>-1</sup> [11]
- D Dilution factor of wastewater by surface water flow (default value) = 10 [11]

$$\text{PEC} = 0.00025 \text{ } \mu\text{g/L}$$

*Note:* Alectinib is at least partially metabolised in the body. Since little is known about the ecotoxicity of these metabolites, it is assumed as a worst case that they have the same ecotoxicological relevance as Alectinib.

### Predicted No Effect Concentration (PNEC)

Chronic studies have been performed for species from three trophic levels, based on OECD Test Guidelines [17]. The lowest No Observed Effect Concentration (NOEC) is 133 µg/L of the 21 d daphnid chronic reproduction study according to OECD 211 [17]. Applying as assessment factor of 10 according to the EMA Guideline [11] this results in a PNEC value of 13.3 µg/L.

$$\text{PNEC} = 133 \text{ } \mu\text{g/L} \div 10 = 13.3 \text{ } \mu\text{g/L}$$

### PEC/PNEC ratio

$$\text{PEC} = 0.00025 \text{ } \mu\text{g/L}$$

$$\text{PNEC} = 13.3 \text{ } \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.00002$$

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [11], a PEC/PNEC ratio of 0.00002 (i.e. <1) means that Alectinib and/or its metabolites are unlikely to represent a risk to the aquatic environment.

## Aquatic Toxicity Data for Alectinib

Study	Guideline	Results	Ref.
Algal growth inhibition test with <i>Raphidocelis subcapitata</i>	OECD 201	72 h EC <sub>50</sub> (growth rate) >11.7 mg/L GMC 72 h EC <sub>50</sub> (yield) >11.7 mg/L GMC 72 h NOEC 11.7 mg/L GMC	[4]
Acute immobilisation test with <i>Daphnia magna</i>	OECD 202	48 h EC <sub>50</sub> >122 mg/L MMC 48 h NOEC 122 mg/L MMC	[5]
Acute toxicity to zebrafish ( <i>Danio rerio</i> )	OECD 203	96 h LC <sub>50</sub> >6.52 mg/L MMC	[6]
<i>Daphnia magna</i> , reproduction test	OECD 211	21 d NOEC (overall) 0.133 mg/L TWM	[7]
Fish, early-life stage toxicity test with zebrafish ( <i>Danio rerio</i> )	OECD 210	36 d NOEC (overall) 10 mg/L NC	[8]
Activated sludge respiration inhibition test	OECD 209	3 h EC <sub>50</sub> >1000 mg/L 3 h NOEC 1000 mg/L	[9]

EC <sub>50</sub>	Concentration of the test substance that results in 50% effect
LC <sub>50</sub>	Concentration of the test substance that results in 50% mortality
NOEC	No observed effect concentration
GMC	Geometric mean measured concentration
MMC	Mean measured concentration
NC	Nominal concentration
TWM	Time-weighted mean measured concentration

## Environmental Fate Data for Alectinib

Study	Guideline	Results	Ref.
Ready biodegradability	OECD 301 F	No degradation with respect to BOD not readily biodegradable	[15]
Aerobic transformation in aquatic sediment systems	OECD 308	Half-life (water) = 1.5–2.3 d Half-life (total system) = 75–273 d	[1] a)
Soil adsorption coefficient	OECD 106	K <sub>oc</sub> = 14921–32878 L/kg	[2] b)
Sludge adsorption coefficient	OECD 106	K <sub>d</sub> = 1473–4294 L/kg K <sub>oc</sub> = 5707–16634 L/kg	[2] b)
Bioaccumulation in Zebrafish ( <i>Danio rerio</i> )	OECD 305	BCF = 146.8–147.7 L/kg BCF <sub>l</sub> = 197.3–198.5 L/kg	[10]

BOD	biochemical oxygen demand
K <sub>oc</sub>	Organic carbon normalised adsorption coefficient
K <sub>d</sub>	Distribution coefficient for adsorption
BCF	Bioconcentration factor
BCF <sub>l</sub>	Bioconcentration factor, normalised to 5% lipids
a)	<i>In conclusion</i> , in water/sediment systems Alectinib was found to rapidly partition from the water phase to the sediment; there it slowly formed several transformation products; there was no indication of mineralisation, however, a slow formation of non-extractable residues was observed
b)	<i>Interpretation</i> : Alectinib adsorbs to both soils and activated sludges. Alectinib can be classified as immobile in soil and sludge

## Physical Chemical Data for Alectinib

Study	Guideline	Results	Ref.
Water solubility	Not specified	46 mg/L (pH 5, 37 °C)	[14]
Dissociation constant	QSAR	pKa = 6.7–7.54 pKa = 11.2–13.7 pKa = 4.4	
n-Octanol/Water Partition Coefficient	OECD 117	log D <sub>OW</sub> = 3.09 (pH 5) log D <sub>OW</sub> = 3.86 (pH 7) log D <sub>OW</sub> = 3.85 (pH 9) log P <sub>OW</sub> = 3.85 (neutral molecule)	[3]

QSAR Quantitative structure–activity relationship models

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