

Environmental Risk Assessment Summary

Vismodegib

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

Vismodegib is used to treat adults with a type of skin cancer, called basal cell carcinoma that has spread to other parts of the body or cannot be treated effectively with surgery or radiation. Vismodegib works by blocking abnormal functioning of the Hedgehog cell signalling pathway. Abnormal activation of this pathway is responsible for tumour development in most basal cell carcinomas [7].

Vismodegib is the active pharmaceutical ingredient used in the Roche product Erivedge.

Major metabolic pathways of Vismodegib involve primary oxidations followed by sequential glucuronidation or sulfation. Orally administered Vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug, the majority of which is recovered in the faeces (82% of the administered dose), with 4.4% of the administered dose recovered in urine [7].

Vismodegib is not readily biodegradable in standard OECD tests over 28 days. In water/sediment systems over 100 days, only partial transformation of Vismodegib was observed. No significant mineralisation (formation of CO₂) was observed.

The PEC/PNEC ratio is 0.00004. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [6], a PEC/PNEC ratio of <1 means that Vismodegib 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:

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

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|---|--|
| A | Total patient consumption of Vismodegib in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [17]) |
| R | Removal rate during sewage treatment = 0.08 (8% 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 [8]; resulting in a consumption of 0.2 mg/inhabitant |
| V | Volume of wastewater per inhabitant and day (default value) = 200 L day ⁻¹ [6] |
| D | Dilution factor of wastewater by surface water flow (default value) = 10 [6] |

$$\text{PEC} = 0.0003 \text{ } \mu\text{g/L}$$

Note: Vismodegib 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 Vismodegib.

Predicted No Effect Concentration (PNEC)

Chronic studies have been performed for species from three trophic levels, based on OECD Test Guidelines. The lowest No Observed Effect Concentration (NOEC) is 69 µg/L of the 72 h algal growth inhibition study according to OECD 201. Applying an assessment factor of 10 according to the EMA Guideline [6], this results in a PNEC value of 6.9 µg/L.

$$\text{PNEC} = 69 \text{ } \mu\text{g/L} / 10 = 6.9 \text{ } \mu\text{g/L}$$

PEC/PNEC ratio

$$\text{PEC} = 0.0003 \text{ } \mu\text{g/L}$$

$$\text{PNEC} = 6.9 \text{ } \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.00004$$

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [6], a PEC/PNEC ratio of 0.00004 (i.e. <1) means that Vismodegib and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Vismodegib

Study	Guideline	Results	Ref.
Algal Growth Inhibition Test with <i>Raphidocelis subcapitata</i>	OECD 201	72 h EC50 (growth rate) 0.118 mg/L 72 h EC50 (yield) 0.099 mg/L 72 h NOEC 0.069 mg/L	[10]
Acute Immobilisation Test with <i>Daphnia magna</i>	OECD 202	48 h EC50 >100 mg/L NC 48 h NOEC = 0.85 mg/L NC	[1]
Acute Toxicity to Zebrafish (<i>Danio rerio</i>)	OECD 203	96 h LC50 >1.5 mg/L NC 96 h NOEC = 1.5 mg/L NC	[11]
<i>Daphnia magna</i> , Reproduction Test	OECD 211	21 d NOEC (overall) = 1.5 mg/L	[12]
Fish, Early-life Stage Toxicity Test with Zebrafish (<i>Danio rerio</i>)	OECD 210	35 d NOEC (overall) = 1.6 mg/L	[13]
Activated Sludge Respiration Inhibition Test	OECD 209	3 h NOEC = 1000 mg/L NC	[14]

EC50 concentration of the test substance that results in 50% effect

NOEC No Observed Effect Concentration

NC Nominal concentration

Environmental Fate Data for Vismodegib

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 F	2.0% after 28 days with respect to biochemical oxygen demand (BOD) not readily biodegradable	[2]
Aerobic Transformation in Aquatic Sediment Systems	OECD 308	Half-life (water) = <4 d Half-life (total system) = 145 – >1000 d	[15] a)
Soil Adsorption Coefficient	OECD 106	Koc = 2129–5001 L/kg	[16] b)
Sludge Adsorption Coefficient	OECD 106	Kd = 199–283 L/kg Koc = 684–895 L/kg	[16] b)

Koc Organic carbon normalised adsorption coefficient

Kd Distribution coefficient for adsorption

- a) *Interpretation:* Vismodegib rapidly distributes from the water to the sediment compartment, where it slowly forms non-extractable bound residues. Vismodegib is not significantly biologically mineralised in Sediment/Water Systems.
- b) *Interpretation:* All single and average Koc values for the three soils and two activated sludges are below the EMA (2006) Guideline regulatory threshold [6] of 10'000 L/kg

Physical Chemical Data for Vismodegib

Study	Guideline	Results	Ref.
Water solubility	OECD 105	0.879 mg/L (pH 6.8, 20 °C)	[4]
Solubility in environmentally relevant ecotoxicity media	OECD 211	1.5 mg/L	[12]
	OECD 210	1.6 mg/L	[13]
Dissociation constant		pKa = 3.4–3.5	[5]
n-Octanol/Water Partition Coefficient	OECD 117	log P _{ow} = 1.59 (pH 7)	[3]

References

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