

## **Environmental Risk Assessment Summary**

### **Baloxavir marboxil**

#### **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**

Baloxavir marboxil is an antiviral medicine for treating and preventing flu in adults and children from 12 years of age. Baloxavir marboxil is the pharmaceutical active substance in the Roche product Xofluza [16].

Baloxavir marboxil is a prodrug and converted to the active substance Baloxavir through metabolism (hydrolysis). Baloxavir selectively inhibits targets necessary for replication of influenza viruses and shows potent inhibitory effects on virus replication.

The Environmental Risk Assessment is performed for the active substance Baloxavir.

Baloxavir marboxil is not readily biodegradable [4]. In a sediment/water study with Baloxavir over 100 days, >90% of the applied radioactivity was observed in the sediment as non-extractable residues (NER) [11].

The PEC/PNEC ratio is 0.002. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [15], a PEC/PNEC ratio of <1 means that Baloxavir 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:

$$\text{PEC (ng/L)} = (\text{MDD} \times 10^3 \times F_{\text{PEN-REFINED}}) \div (V \times D)$$

MDD	Maximal daily dose (Baloxavir marboxil) = 80 mg/d Maximal daily dose (Baloxavir) = 67.7 mg/d
$F_{\text{PEN-REFINED}}$	Based on prevalence of the diseases: 0.00055
V	Volume of wastewater per inhabitant and day (default value) = 200 L day <sup>-1</sup> [15]
D	Dilution factor of wastewater by surface water flow (default value) = 10 [15]

$$\text{PEC} = 0.019 \text{ } \mu\text{g/L (as Baloxavir)}$$

*Note:* Baloxavir 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 Baloxavir.

## Predicted No Effect Concentration (PNEC)

Chronic studies have been performed for Baloxavir for species from three trophic levels, based on OECD Test Guidelines [17]. The lowest NOEC is 0.092 mg/L (92  $\mu\text{g/L}$ ) assessed in a toxicity test with green algae [6]. Applying an assessment factor of 10 according to the EMA Guideline [15], this results in a PNEC value of 9.2  $\mu\text{g/L}$ .

$$\text{PNEC} = 92 \text{ ng/L} / 10 = 9.2 \text{ } \mu\text{g/L}$$

## PEC/PNEC ratio

$$\text{PEC} = 0.019 \text{ } \mu\text{g/L}$$

$$\text{PNEC} = 9.2 \text{ } \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.002$$

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [15], a PEC/PNEC ratio of 0.002 (i.e. <1) means that Baloxavir and/or its metabolites are unlikely to represent a risk to the aquatic environment.

### Aquatic Toxicity Data for Baloxavir marboxil (BVM) and Baloxavir (BV)

Study	Guideline	Results	Test item	Ref.
Growth inhibition test with green algae ( <i>Desmodesmus subspicatus</i> )	OECD 201	72 h EC50 (growth rate) 9.28 mg/L MMC 72 h EC50 (yield) 4.76 mg/L MMC 72 h EC10 (growth rate) 4.20 mg/L MMC 72 h EC10 (yield) 2.02 mg/L MMC 72 h NOEC 1.75 mg/L MMC	BVM	[1]
Growth inhibition test with green algae ( <i>Raphidocelis subcapitata</i> )	OECD 201	72 h EC50 (growth rate) >3.2 mg/L MMC 72 h EC50 (yield) 0.46 mg/L MMC 72 h NOEC 0.092 mg/L MMC	BV	[6]
Acute immobilisation test with <i>Daphnia magna</i>	OECD 202	48 h EC50 >17.4 mg/L IMC 48 h NOEC 17.4 mg/L IMC	BVM	[2]
<i>Daphnia magna</i> , Reproduction Test	OECD 211	21 d EC10 1.5 mg/L MMC 21 d NOEC 0.44 mg/L MMC	BV	[7]
Acute toxicity to zebrafish ( <i>Danio rerio</i> )	OECD 203	96 h LC50 >10.6 mg/L MMC 96 h NOEC 10.6 mg/L MMC	BVM	[3]
Fish, early-life stage toxicity test with fathead minnow ( <i>Pimephales promelas</i> )	OECD 210	36 d EC10 (hatching success) 0.11 mg/L MMC	BV	[8]
Chronic toxicity to sediment-dwelling <i>Chironomus riparius</i>	OECD 218	28 d EC50 >1000 mg/kg NC 28 d LOEC 1000 mg/kg NC 28 d NOEC 320 mg/kg NC	BV	[9]
Activated sludge respiration inhibition test	OECD 209	3 h EC50 56 mg/L NC	BV	[10]

EC10 concentration of the test substance that results in 10% effect

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

NOEC No observed effect concentration

IMC Initially measured concentration

MMC Mean measured concentration

NC Nominal concentration

### Environmental Fate Data for Baloxavir marboxil (BVM) and Baloxavir (BV)

Study	Guideline	Results	Test item	Ref.
Ready biodegradability	OECD 301 F	<u>BOD ÷ ThOD (mineralisation)</u> 0% after 28 d	BVM	[4]
Aerobic transformation in aquatic sediment systems	OECD 308	DT50 (total system) >120 d	BV	[11]
Soil Adsorption Coefficient	OECD 106	K <sub>OC</sub> = 107,000–186,000 L/kg	BV	[12]
Sludge Adsorption Coefficient	OECD 106	K <sub>OC</sub> = 16,200–44,000 L/kg	BV	[12]

BOD Biochemical oxygen demand

ThOD Theoretical oxygen demand

DT50 Half life

K<sub>OC</sub> Adsorption distribution coefficient, corrected for organic carbon content

TOC Total organic carbon

### Physical Chemical Data for Baloxavir marboxil (BVM) and Baloxavir (BV)

Study	Guideline	Results	Test item	Ref.
Water solubility	OECD 105	5.1 mg/L (pH 7, 20 °C)	BV	[13]
n-Octanol-water distribution coefficient	OECD 117	logD <sub>OW</sub> 2.5 (pH 5, 25 °C)	BVM	[5]
	OECD 117	logD <sub>OW</sub> 2.5 (pH 7, 25 °C)	BVM	[5]
	OECD 117	logD <sub>OW</sub> 2.5 (pH 9, 25 °C)	BVM	[5]
	OECD 107	logD <sub>OW</sub> 2.0 (pH 5, 20 °C)	BV	[14]
	OECD 107	logD <sub>OW</sub> 2.0 (pH 7, 20 °C)	BV	[14]
	OECD 107	logD <sub>OW</sub> 1.1 (pH 9, 20 °C)	BV	[14]

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