

Environmental Risk Assessment Summary

Benserazide hydrochloride

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

The Roche product Madopar is a combination of two active pharmaceutical ingredients, Levodopa and Benserazide hydrochloride, in the ratio 4:1. Madopar is used to treat Parkinson's disease [8].

Levodopa is the metabolic precursor of dopamine, whereas Benserazide hydrochloride is a peripheral decarboxylase inhibitor [4]. Administration of a peripheral decarboxylase inhibitor, which blocks the extracerebral decarboxylation of levodopa, in conjunction with levodopa has significant advantages; these include reduced gastro-intestinal side-effects, a more rapid response at the initiation of therapy and a simpler dosage regimen. [4].

Benserazide hydrochloride is well absorbed and extensively metabolised in the gut epithelium and liver to trihydroxybenzylhydrazine. The metabolites of benserazide are mainly excreted by urinary pathway [4].

Benserazide hydrochloride is not readily biodegradable [1]. In an inherent biodegradability test according to OECD 302 B an elimination of 93% after 14 days was observed [9]. This elimination is presumably only due to adsorption to the activated sludge and not due to biodegradation. However, significant hydrolysis is observed. Although Benserazide hydrochloride could not be mineralized in the ready biodegradability test, the parent compound was not detectable anymore by compound specific analysis after 28 days.

The PEC/PNEC ratio is 0.13. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [4], a PEC/PNEC ratio of ≤ 1 means that Benserazide hydrochloride 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 Benserazide hydrochloride in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [10])
- R Removal rate during sewage treatment (default value) = 0 [6]
- P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [7]; resulting in a consumption of 3.5 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]

$$\text{PEC} = 0.138 \text{ } \mu\text{g/L}$$

Note: Benserazide hydrochloride 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 Benserazide hydrochloride.

Predicted No Effect Concentration (PNEC)

Acute studies have been performed for species from three trophic levels, based on OECD Test Guidelines. The lowest EC50/LC50 is 1.08 mg/L of the 72 h growth inhibition test with the green alga *Desmodesmus subspicatus* according to OECD 201 [2]. Applying an assessment factor of 1000 according to the REACH Guidance [5] results in a PNEC value of 1.08 µg/L.

$$\text{PNEC} = 1080 \text{ } \mu\text{g/L} / 1000 = 1.08 \text{ } \mu\text{g/L}$$

PEC/PNEC ratio

$$\text{PEC} = 0.138 \text{ } \mu\text{g/L}$$

$$\text{PNEC} = 1.08 \text{ } \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.13$$

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 0.13 (i.e. ≤1) means that Benserazide hydrochloride and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Benserazide hydrochloride

Study	Guideline	Results	Ref.
Algal growth inhibition test with the green alga <i>Desmodesmus subspicatus</i>	OECD 201	72 h EC ₅₀ (growth rate) = 2.66 mg/L NC 72 h EC ₅₀ (yield) = 1.08 mg/L NC 72 h NOEC = 0.299 mg/L NC	[2]
Acute Immobilisation Test with <i>Daphnia magna</i>	OECD 202	48 h EC ₅₀ = 18.8 mg/L NC 48 h NOEC = 6.25 mg/L NC	[3]
Acute toxicity to rainbow trout (<i>Oncorhynchus mykiss</i>)	OECD 203	96 h LC ₅₀ = 316 mg/L NC 96 h NOEC = 200 mg/L NC	[9]
Bacteria toxicity (toxicity control in ready biodegradability test)	OECD 301 F	14 d NOEC = 50 mg/L	[1]

EC₅₀ Concentration of the test substance that results in 50% effect
 LC₅₀ Concentration of the test substance that results in 50% mortality
 NC Nominal concentration
 NOEC No Observed Effect Concentration

Environmental Fate Data for Benserazide hydrochloride

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 F	0% after 28 days (BOD/ThOD) 48% after 28 days (DOC elimination) 100% after 28 days (removal of parent compound, analysed by HPLC) Not readily biodegradable	[1]
Inherent Biodegradability Test (DOC elimination)	OECD 302 B	84% after 1 day 92% after 7 days 93% after 14 days 93% after 28 days	[9]
Hydrolysis		52% after 5 days (22 °C, in the dark)	[1]
Photodegradation		58% after 5 days (22 °C, light)	[1] a)

BOD Biochemical oxygen demand
 DOC Dissolved organic carbon
 ThOD Theoretical oxygen demand
 a) Presumably only hydrolysis takes place

Physical Chemical Data for Benserazide hydrochloride

Study	Guideline	Results	Ref.
Water solubility		335 g/L (20 °C)	[9]
n-Octanol/Water Partition Coefficient		log P _{OW} <0 (calculated)	[9]

References

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- [7] Eurostat. Population data. <https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data>
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- [10] IQVIA MIDAS Quantum, Q1 2018