Environmental Risk Assessment Summary
Mircera

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

C.E.R.A. (Continuous Erythropoiesis Receptor Activator) is methoxy polyethylene glycol-epoetin beta (mono-pegylated epoetin-b), consisting of recombinant human epoetin-b protein (EPO) which is bound covalently to a linear methoxy-polyethylene glycol, with maintenance of its own glycosylation. C.E.R.A. is the pharmaceutical active substance in the Roche product Mircera [4].

The active substance in Mircera, methoxy polyethylene glycol-epoetin beta, works like natural erythropoietin (EPO) to stimulate red blood cell production, because it can attach itself to the same receptors as EPO. However, the way it interacts with the receptor is slightly different from natural EPO, which gives it a longer effect. It is also cleared from the body less quickly. As a result, Mircera can be given less often than natural EPO [3]. Pharmacokinetic studies for absorption, distribution, metabolism, and excretion (ADME) sowed that C.E.R.A is in part metabolised through proteases cleaving erythropoietin, with degradation of the protein moiety to non-recognisable, biologically inactive fractions. However, a non-quantified part of C.E.R.A. was found to be excreted unchanged (Roche internal information).

Mircera is not readily biodegradable. After 28 days a mineralisation of 57% was observed. Primary degradation was complete after 4 days [9]. It can be assumed that the protein moiety (EPO) is degraded.

The PEC/PNEC ratio is 0.0000007. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [2], a PEC/PNEC ratio of ≤1 means that Mircera 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:

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

MDD	Maximal daily dose = 0.8 mg/d	
$F_{PEN\text{-}REFINED}$	Refined market penetration factor [2]:	
	$F_{PEN\text{-}REFINED} = (P_{REGION} \times t_{TREATMENT} \times n_{TREATMENT}) \div Nd$	
	P_{REGION}	Prevalence (default value) = 0.01 [2]
	$t_{TREATMENT}$	Duration of one treatment period = 1 day
	$n_{TREATMENT}$	Number of treatments per year = 12 (once, monthly)
	Nd	Number of days per year = 365
V	Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [2]	
D	Dilution factor of wastewater by surface water flow (default value) = 10 [2]	

PEC = 0.00013 µg/L

Note: Mircera 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 Mircera.

Predicted No Effect Concentration (PNEC)

The PNEC is derived from the lowest EC50/LC50 from acute studies with algae, *Daphnia* and fish according to OECD Test Guidelines [5]. All EC50/LC50 values are >200 mg/L. Applying an assessment factor of 1000 according to the REACH Guidance [1] results in a PNEC value of 200 µg/L.

PNEC = 200000 mg/L / 1000 = 200 µg/L

PEC/PNEC ratio

PEC = 0.00013 µg/L
PNEC = 200 µg/L

PEC/PNEC = 0.0000007

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [2], a PEC/PNEC ratio of 0.0000007 (i.e. ≤1) means that Mircera and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Mircera

Study	Guideline	Results	Ref.
Algal growth inhibition test with the green alga *Desmodesmus subspicatus*	OECD 201	72 h EC50 >200 mg/L NC 72 h NOEC 200 mg/L NC	[6]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 >200 mg/L NC 48 h NOEC 200 mg/L NC	[7]
Acute toxicity to zebrafish (*Danio rerio*)	OECD 203	96 h LC50 >200 mg/L NC 96 h NOEC 200 mg/L NC	[8]
Microbial inhibition (toxicity control in biodegradation test)	OECD 301 F	14 d NOEC 100 mg/L NC	[9]

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

Environmental Fate Data for Mircera

Study	Guideline	Results	Ref.
Ready biodegradability	OECD 301 F	BOD ÷ COD (mineralisation) 57% after 28 d Primary degradation (LC-UV) 100% after 4 d	[9]

BOD Biochemical oxygen demand
COD Chemical oxygen demand

Physical Chemical Data for Mircera

Study	Guideline	Results	Ref.
Water solubility	NA	>17500 mg/L	[4]

References

[1] European Chemicals Agency (ECHA)(2008): Guidance on information requirements and chemical safety assessment Chapter R.10: Characterisation of dose [concentration]-response for environment

[2] European Medicines Agency (EMA) (2006/2015): Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 01 June 2006, EMA/CHMP/SWP/447/00 corr 2

[3] European Medicines Agency (EMA) (2012): Mircera – EPAR summary for the public. EMA/CHMP/227862/2012. https://www.ema.europa.eu/en/documents/overview/mircera-epar-summary-public_en.pdf

[4] F. Hoffmann-La Roche Ltd (2017): Safety data sheet for Mircera, 16 December 2017. https://www.roche.com/sustainability/environment/safety_data_sheets-row.htm

[5] Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for the Testing of Chemicals. http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm

[6] RCC Ltd, on behalf of F. Hoffmann-La Roche Ltd (2006): RO053821, Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test. RCC study no. A03014

[7] RCC Ltd, on behalf of F. Hoffmann-La Roche Ltd (2006): RO053821, Acute toxicity to *Daphnia magna* in a 48-hour immobilisation test. RCC study no. A03071

[8] RCC Ltd, on behalf of F. Hoffmann-La Roche Ltd (2006): RO053821, Acute toxicity to zebrafish (*Danio rerio*) in a 96-hour static test. RCC study no. A03104

[9] RCC Ltd, on behalf of F. Hoffmann-La Roche Ltd (2006): RO053821, ready biodegradability and primary biodegradation in a manometric respirometry test. RCC study no. A03137