Environmental Risk Assessment Summary
Valganciclovir

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

Valganciclovir is used for the treatment and prevention of cytomegalovirus and other herpesvirus infections. Valganciclovir, the L-valine ester and prodrug of Ganciclovir, was developed because it shows much improved oral bioavailability compared with Ganciclovir [17].

Valganciclovir [5] is the active pharmaceutical ingredients used in the Roche product Valcyte. Ganciclovir [6] is the active pharmaceutical ingredient in the former Roche product Cymevene.

After oral ingestion, Valganciclovir is rapidly hydrolyzed to Ganciclovir and L-valine by enteric and hepatic esterases; there is essentially no further metabolism, and Ganciclovir is excreted by the urinary pathway [17]. Hence environmentally relevant data is only listed for Ganciclovir.

Results from non-standard tests suggest that Ganciclovir is neither readily nor inherently biodegradable [1]. In water/sediment systems over 100 days significant mineralisation (formation of CO_2) of Ganciclovir of 37.3–69.5% was observed, indicating that Ganciclovir is not a persistent compound [15].

The PEC/PNEC ratio is 0.01. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [3], a PEC/PNEC ratio of <1 means that Ganciclovir 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) = (A × 109 × (1–R)) ÷ (365 × P × V × D)

A Total patient consumption of Ganciclovir (as the sum of Ganciclovir and Valganciclovir) in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [7]

R Removal rate during sewage treatment (default value) = 0 [3]

P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [4]; resulting in a consumption of 9.6 mg/inhabitant

V Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [3]

D Dilution factor of wastewater by surface water flow (default value) = 10 [3]

PEC = 0.012 µg/L

Predicted No Effect Concentration (PNEC)

Chronic studies have been performed for species from three trophic levels, based on OECD Test Guidelines [10]. The lowest No Observed Effect Concentration (NOEC) is 0.012 mg/L (12 µg/L) assessed in a fish partial life cycle test with Fathead minnow (*Pimephales promelas*), consisting of a fish short-term reproduction test (OECD 229) directly followed by a fish partial life cycle test (OECD 210) [13]. Applying an assessment factor of 10 according to the EMA Guideline [3], this results in a PNEC value of 1.2 µg/L.

PNEC = 12 µg/L / 10 = 1.2 µg/L

PEC/PNEC ratio

PEC = 0.012 µg/L
PNEC = 1.2 µg/L

PEC/PNEC = 0.01

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [3], a PEC/PNEC ratio of 0.01 (i.e. <1) means that Ganciclovir and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Ganciclovir

Study	Guideline	Results	Ref.
Algal Growth Inhibition Test with *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) >109 mg/L GMC 72 h EC50 (yield) >109 mg/L GMC 72 h NOEC 109 mg/L GMC	[11]
Daphnia magna, Reproduction Test	OECD 211	21 d NOEC (overall) 3.3 mg/L GMC, HTC	[12]
Fish, Partial Life Cycle Test with Fathead minnow (*Pimephales promelas*)	OECD 229 / OECD 210	F_0 (short-term reproduction phase) 21 d NOEC 1.1 mg/L MMC, HTC F_1 (early life stage test phase) 35 d NOEC 0.012 mg/L MMC F_0 and F_1 generations NOEC (overall) 0.012 mg/L MMC	[13]
Activated Sludge Respiration Inhibition Test	OECD 209	3 h NOEC = 1000 mg/L	[14]

EC50 concentration of the test substance that results in 50% effect
NOEC No Observed Effect Concentration
F_0, F_1 Generations
GMC Geometric mean concentration
MMC Mean measured concentration
HTC Highest tested concentration

Environmental Fate Data for Ganciclovir

Study	Guideline	Results	Ref.
Non-standard tests using different sources of inoculum (% ^{14}C produced within 28 days)	NA	1. Activated sludge (aerobic): 1.8% 2. Activated sludge + digester sludge (aerobic/anaerobic): 3.4% 3. Activated sludge (abiotic): 0.2% 4. Secondary effluent (aerobic): 1.6% 5. Soil suspension (aerobic): 56.8% 6. River water/sediment (aerobic): 34.2% 7. Digester sludge (anaerobic): 0.9%	[1]
Aerobic Transformation in Aquatic Sediment Systems	OECD 308	Half-life (water) 8–10 d Half-life (total system) 14–18 d $^{14}CO_2$ evolution 37.3–69.5% (100 d)	[15] a)
Adsorption Coefficient	OECD 106	K_d 1.17–1.62 L/kg K_{OC} 83.65–105.58 L/kg	[16] b)

K_d Distribution coefficient for adsorption
K_{OC} Organic carbon normalised adsorption coefficient
a) *Interpretation* Ganciclovir proved not to be a persistent compound
b) *Interpretation*: The K_{OC} is below the regulatory threshold of 10,000 L/kg

Physical Chemical Data for Ganciclovir

Study	Guideline	Results	Ref.
Water solubility	OECD 105	2670 mg/L (pH 7.0)	[9]
Dissociation constant		pK_a1 9.57 (acidic group), 24 °C pK_a2 2.2 (basic group, extrapolated)	[8]
n-Octanol/Water Partition Coefficient	OECD 107	log P_{OW} -1.95, 25 °C (unionised pH 5 and 7, average)	[2]

References

[1] ABC Laboratories, Inc, on behalf of Syntex Research, Palo Alto, California (1993): Survey of Inoculum Sources for Biodegradation of ^{14}C-Ganciclovir. ABC Laboratories' Project ID #40403

[2] Carlson T, Licato N (1991): n-Octanol-water distribution ratio of ganciclovir in aqueous buffers. Analytical and Environmental Research, Syntex Discovery Research, Palo Alto, CA, USA

[3] 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

[4] Eurostat. Population data. https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data

[5] F. Hoffmann-La Roche Ltd (2021): Safety data sheet for Valganciclovir, 14 January 2021. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[6] F. Hoffmann-La Roche Ltd (2021): Safety data sheet for Ganciclovir, 14 January 2021. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[7] IQVIA MIDAS Quantum, Q1 2018

[8] Nicholson V, Licato N (1992): Dissociation constant of ganciclovir. Analytical and Environmental Research, Syntex Discovery Research, Palo Alto, CA, USA

[9] Nicholson V, Licato N (1992): Solubility of ganciclovir in aqueous buffers. Analytical and Environmental Research, Syntex Discovery Research, Palo Alto, CA, USA

[10] Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for the Testing of Chemicals

[11] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: Inhibition of Growth to the Alga *Pseudokirchneriella subcapitata*. Smithers Viscient (ESG) study no. 3200781

[12] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: *Daphnia magna* Reproduction Test. Smithers Viscient (ESG) study no. 3200782

[13] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: Fish Partial Life Cycle Test (*Pimephales promelas*). Smithers Viscient (ESG) study no. 3200783

[14] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: Activated Sludge Respiration Inhibition Test. Smithers Viscient (ESG) study no. 3200788

[15] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: Degradation in Water-Sediment Systems under Aerobic Conditions. Smithers Viscient (ESG) study no. 3200729

[16] Smithers Viscient (ESG) Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2015): Ganciclovir: Adsorption/Desorption in Two Soils, Two Activated Sludges and Two Sediments. Smithers Viscient (ESG) study no. 3200728

[17] Straub JO (2017): Combined environmental risk assessment for the antiviral pharmaceuticals ganciclovir and valganciclovir in Europe. Environ Toxicol Chem. 36(8):2205-2216