Environmental Risk Assessment Summary
Trastuzumab emtansine

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

Trastuzumab emtansine (Trastuzumab-DM1, T-DM1) is an antibody-drug conjugate engineered to deliver potent chemotherapy directly to HER2-positive cancer cells, potentially limiting damage to healthy tissues. It combines two anti-cancer properties joined together by a stable linker: the HER2-targeting properties of trastuzumab (the active ingredient in Herceptin) and the chemotherapy agent DM1 (a maytansine derivative) (Roche Product Information). T-DM1 is the pharmaceutical active substance in the Roche product Kadcyla [8]. Kadcyla is approved as a single agent in over 100 countries, including the US and EU, for the treatment of people with HER2-positive advanced breast cancer who have previously received Herceptin and taxane-based chemotherapy, either separately or in combination (Roche Product Information). T-DM1 is transported in its entirety to its site of action, where the antibody-drug conjugate is internalised into the HER2-positive cell. Following endocytosis the conjugate is split through proteolysis, releasing the active moiety MCC-DM1 (possibly with small peptide residuals, i.e. lys-MCC-DM1) to block cell division through the tubulin-inhibitory action of the DM1 portion. It is the same MCC-DM1 part, possibly with small peptide residuals (such as lys-MCC-DM1), that is excreted both in mammals and human patients [11]. MCC-DM1 makes up just below 2% of the whole molecular mass of T-DM1.

The antibody-drug conjugate T-DM1 is readily biodegradable [1]. MCC-DM1, however, is not inherently biodegradable [6]. It is therefore expected that through both patient metabolism and biodegradation in wastewater treatment, no whole T-DM1 will reach the environment but only MCC-DM1, possibly with small peptide residuals.

The PEC/PNEC ratio for MCC-DM1 is estimated to be 0.00068. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines

Agency [7], a PEC/PNEC ratio of <1 means that MCC-DM1 is unlikely to represent a risk to the aquatic environment.

Predicted Environmental Concentration (PEC)

The PEC for MCC-DM1 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:	T-DM1 = 252 mg/d (3.6 mg/kg/d, body weight 70 kg) MCC-DM1 (2% of T-DM1) = 5.0 mg/d
$F_{PEN\text{-}REFINED}$	Refined market penetration factor [7]:	
	$F_{PEN\text{-}REFINED} = (P_{REGION} \times t_{TREATMENT} \times n_{TREATMENT}) \div Nd$	
	P_{REGION}	Prevalence = 0.00057 (breast cancer, 5-year prevalence [10] + HER2 positivity [11])
	$t_{TREATMENT}$	Duration of one treatment period = 1 day
	$n_{TREATMENT}$	Number of treatments per year = 17.3 (every 3 weeks)
	Nd	Number of days per year = 365
V	Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [7]	
D	Dilution factor of wastewater by surface water flow (default value) = 10 [7]	

PEC (MCC-DM1) = 0.000068 µg/L

Predicted No Effect Concentration (PNEC)

No ecotoxicity data are available for MCC-DM1. Therefore, a default PNEC was used to estimate the risk of MCC-DM1 for surface water.

Default or *de minimis* PNECs can be adopted from recent retrospective analyses of available aquatic toxicity data with pharmaceuticals. Gunnarsson *et al.*, 2019 [9] reviewed the range of chronic PNECs for 133 compounds and found that for more than 90% these PNECs were >0.01 µg/L and for all hydrophilic ($logD_{OW}$ <3) substances the PNECs were >0.1 µg/L. When endocrine active substances (EASs) were removed from the analysis more than 90% had PNECs >0.1 µg/L irrespective of hydrophobicity. A similar analysis was carried out on 195 APIs using PNECs from the Swedish Fass.se database of pharmaceuticals (available at Fass.se and reported in Roos *et al.*, 2012 [12]). These data demonstrate that in more 90% of cases the PNECs reported in Fass.se were ≥0.1 µg/L.

Therefore, the default PNEC for MCC-DM1 was set to 0.1 µg/L.

PEC/PNEC ratio

PEC (MCC-DM1) = 0.000068 µg/L
PNEC (MCC-DM1) = 0.1 µg/L

PEC/PNEC = 0.00068

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [7], a PEC/PNEC ratio of 0.00068 (i.e. <1) means that MCC-DM1 is unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data

Study	Guideline	Results	Ref.
T-DM1			
Algal growth inhibition test with the green alga *Desmodesmus subspicatus*	OECD 201	72 h EC50 (growth rate) >100 mg/L NC 72 h EC50 (yield) 100 mg/L NC 72 h NOEC <100 mg/L NC	[2]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 >100 mg/L NC 48 h NOEC 100 mg/L NC	[3]
Acute toxicity to guppy (*Poecilia reticulata*)	OECD 203	96 h LC50 >100 mg/L NC 96 h NOEC <100 mg/L NC	[4]
Microbial inhibition (toxicity control in biodegradation test)	OECD 301 F	14 d NOEC 49.5 mg/L NC	[1]
MCC-DM1			
Microbial inhibition (toxicity control in biodegradation test)	OECD 302 C	28 d NOEC 30 mg/L NC	[6]

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

Study	Guideline	Results	Ref.
T-DM1			
Ready biodegradability	OECD 301 F	BOD ÷ ThOD (mineralisation) 84% after 28 d 68% at the end of the 10-d window DOC elimination (removal) 98% after 28 day	[1]
MCC-DM1			
Inherent biodegradability	OECD 302 C	BOD ÷ ThOD (mineralisation) 6% after 28 d DOC elimination (removal) 79% after 28 day	[6]

BOD Biochemical oxygen demand
ThOD Theoretical oxygen demand
DOC Dissolved organic carbon

Physical Chemical Data

Study	Guideline	Results		Ref.
MCC-DM1				
n-Octanol/water distribution coefficient ($logD_{OW}$)	OECD 117	Peak 1:	0.50–0.56 at pH 5 (25 °C)	[5]
			1.15–1.29 at pH 7 (25 °C)	
			0.57–0.62 at pH 9 (25 °C)	
		Peak 2:	0.56–0.61 at pH 5 (25 °C)	
			1.17–1.31 at pH 7 (25 °C)	
			0.65–0.69 at pH 9 (25 °C)	

References

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