# Environmental Risk Assessment Summary
# Emicizumab

## 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.

The EMA Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products [5] requires an ERA for the Marketing Authorisation Application (MAA) of all new medicinal products in the European Union. For proteins and peptides, however, the 'ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment'.

## Summary

Emicizumab is a recombinant bispecific monoclonal antibody produced by biotechnology. It is the active pharmaceutical ingredient used in the Roche product Hemlibra [7].

Emicizumab is a medicine used to prevent or reduce bleeding in patients with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII). It is used in patients who have developed factor VIII inhibitors, which are antibodies in the blood that act against factor VIII medicines and prevent them from working properly [6]

A Manometric Respirometry Test according to OECD guideline no. 301 F showed that formulated Emicizumab (including excipients) is readily biodegradable [1]. Additionally, as supporting information, acute ecotoxicity limit tests with green algae [2], daphnids [3] and fish [4] consistently showed no adverse effects at the only tested concentration of 100 mg/L nominal concentration relating to the active substance Emicizumab.

Considering human metabolism, rapid biodegradability and acute ecotoxicological properties of Emicizumab, no exposure levels of concern to the environment are to be expected. This confirms the general finding that monoclonal antibodies and other protein or peptide active pharmaceutical substances are not expected to pose any risk to the environment [8].

## Aquatic Toxicity Data for Emicizumab

| Study | Guideline | Results | Ref. |
|---|---|---|---|
| Algal Growth Inhibition Test with *Desmodesmus subspicatus* | OECD 201 | 72 h EC50 (growth rate) >100 mg/L NC<br>72 h EC50 (yield) >100 mg/L NC<br>72 h NOEC = 100 mg/L NC | [2] |
| Acute Immobilisation Test with *Daphnia magna* | OECD 202 | 48 h EC50 >100 mg/L NC<br>48 h NOEC = 100 mg/L NC | [3] |
| Acute Toxicity to zebrafish (*Danio rerio*) | OECD 203 | 96 h LC50 >100 mg/L NC | [4] |

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 Emicizumab

| Study | Guideline | Results | Ref. |
|---|---|---|---|
| Ready Biodegradability Test | OECD 301 F | BOD/ThOD (mineralisation)<br>99% after 28 days<br>90% at the end of the 10-day window<br>Readily biodegradable<br><br>DOC elimination<br>98% after 28 days | [1] |

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

## References


[1] Arcadis Schweiz Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2017): Emicizumab solution. Ready biodegradability – evaluation of the aerobic biodegradability in an aqueous medium: manometric respirometry test. ACH study no. A16–01179

[2] Arcadis Schweiz Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2016): Emicizumab solution. Fresh water algal growth inhibition test with *Desmodesmus subspicatus*; limit test with 100 mg Emicizumab/l. ACH study no. A16–01176

[3] Arcadis Schweiz Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2016): Emicizumab solution. 48-Hour acute toxicity to *Daphnia magna*; limit test with 100 mg Emicizumab/l. ACH study no. A16–01177

[4] Arcadis Schweiz Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2016): Emicizumab solution. 96-Hour acute toxicity to *Danio rerio* (zebrafish); limit test with 100 mg Emicizumab/l. ACH study no. A16–01178

[5] 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

[6] European Medicines Agency (EMA) (2018): EPAR summary for the public. Hemlibra / Emicizumab. EMA/67076/2018, February 2018

[7] F. Hoffmann-La Roche Ltd (2020): Safety data sheet for Hemlibra, 16 January 2020. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[8] Straub JO (2010): Protein and Peptide Therapeuticals: An Example of "Benign by Nature" Active Pharmaceutical Ingredients. *In* Kümmerer K, Hempel M, eds: Green and Sustainable Pharmacy. Springer, Heidelberg, pp 127–133