Environmental Risk Assessment Summary
Phytomenadione

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 [2] requires an ERA for the Marketing Authorisation Application (MAA) of all new medicinal products in the European Union. In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), 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

Phytomenadione is a synthetic vitamin K1 analogue. It is the active pharmaceutical ingredient used in the Roche product Konakion MM [2].

In adults, Konakion MM is indicated as an antidote to anticoagulant drugs of the coumarin type in the treatment of haemorrhage or threatened haemorrhage, associated with a low blood level of prothrombin or factor VII. In neonates and infants Konakion MM Paediatric is indicated for the prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) [1].

Half-lifes ranging from 3 to 14 hours have been reported. Under normal conditions, 30-40% of the absorbed phytomenadione is excreted via the bile into the faeces, while approximately 15% is excreted in the urine as water soluble metabolites. Less than 10 % of a dose is excreted unchanged in the urine [5].

As supporting information, acute ecotoxicity tests with cyanobacteria and green algae [6], and fish [3] consistently showed no significant adverse effects of Phytomenadione. While these tests are only acute (except for the algae), they do underpin a low risk for unexpected aquatic ecotoxicity of Phytomenadione.

Aquatic Toxicity Data for Phytomenadione

Study	Guideline	Results	Ref.
Growth inhibition test with the green alga *Raphidocelis subcapitata*	NA	5 d LOEC 45.1 mg/L	[6]
Growth inhibition test with the green alga *Pediastrum simplex*	NA	5 d LOEC 45.1 mg/L	[6]
Growth inhibition test with the cyanobacteria *Anabaena* sp. LP 691	NA	5 d LOEC 45.1 mg/L	[6]
Growth inhibition test with the cyanobacteria *Oscillatoria chalybea*	NA	5 d LOEC 4.51 mg/L	[6]
Acute Toxicity to rainbow trout (*Oncorhynchus mykiss*)	OECD 203	96 h LC50 >100 mg/L 96 h NOEC 100 mg/L	[3]

LC50 concentration of the test substance that results in 50% mortality
LOEC Lowest Observed Effect Concentration
NOEC No Observed Effect Concentration

References

[1] electronic Medicines Compendium (eMC). https://www.medicines.org.uk/emc/
[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] F. Hoffmann-La Roche Ltd, Basel, Switzerland (1994): 96-Hour acute toxicity test with Vitamin K1 in rainbow trout. PSU study no. 92/9-FT
[4] F. Hoffmann-La Roche Ltd (2017): Safety data sheet for Konakion MM, 6 December 2017. https://www.roche.com/sustainability/environment/safety_data_sheets-row.htm
[5] International Agency for Research on Cancer (IARC) (2000): IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 76. Some Antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents
[6] Schrader KK, de Regt MQ, Tidwell PR, Tucker CS, Duke SO (1998): Bull Environ Contam Toxicol. 60(4):651-658