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Environmental Risk Assessment
NEUPRO®

Introduction

The PEC:PNEC ratios indicate that Rotigotine is unlikely to be a concern for the aquatic environment and the risk is classified at a low level.

Rotigotine is not readily biodegradable.

Rotigotine is unlikely to bioaccumulate to any significant extent.

Rotigotine is rapidly degraded in soil under aerobic conditions to unextractable residues.

PEC – Revised Predicted Environmental Concentration

Total PEC for all indications = 0,0372 µg/L

Parkinson's disease

PEC= 0,02025 µg/L

$$PEC_{SURFACE\ WATER} = \frac{Dose_{A.I.} * F_{PEN}}{WASTEW_{INH} * Dilution}$$

Where,

- DoseA.I.: Maximum daily dose of active ingredient consumed per inhabitant (18 mg),
- FPEN: Market penetration factor (0,00225)
- WASTEWINH: Amount (litres) of wastewater per inhabitant per day (Default = 200 L*inh-1*d-1)
- Dilution: Dilution factor (Default = 10)

For degenerative conditions such as Parkinson's disease, prevalence in the target group (age 65+) is up to 1.5%, therefore:

- On a total population basis (i.e. 65+ age group about 15% of total), the prevalence is reduced to 0.225%. (0,015*0,15=0,225).
- Thus, on the basis of disease prevalence, Fpen for a new treatment for Parkinson's disease (early and advanced stages), is likely to be around 0.225% instead of the default Fpen value of 1%.

Restless Leg syndrome

PEC= 0,0169 µg/L

$$PEC_{SURFACE\ WATER} = \frac{Dose_{A.I.} * F_{PEN}}{WASTEW_{INH} * Dilution}$$

Where,

- DoseA.I.: Maximum daily dose of active ingredient consumed per inhabitant (3.38 mg),
- FPEN: Market penetration factor (0,01)
- WASTEWINH: Amount (litres) of wastewater per inhabitant per day (Default = 200 L*inh-1*d-1)
- Dilution: Dilution factor (Default = 10)

PNEC – Predicted No-Effect Concentration

PNEC = 0.105 µg/L

Chronic toxicity studies have been performed for species from three trophic levels of the aquatic compartment following OECD guidelines which are universally accepted.

The PNECWATER was determined based on the lowest NOEC result from the base set chronic toxicity testing and applying an assessment factor of 10.

For Rotigotine, the lowest end point was on Fish early life stage (Fathead minnows) which had a 28 day NOEC of 0.00105 mg/L therefore PNEC=0,00105/10=0.105 µg/L

Environmental Risk Level – PEC/PNEC ratio

PEC/PNEC = 0,0372/0,105 = 0,35

The PEC/PNEC ratio is below 1. This is below the trigger of 1 and indicates that Rotigotine is unlikely to represent a risk to the aquatic environment and the risk is classified at a low level.

Additionally, the PEC value that has been used to calculate the PEC:PNEC ratio is still an overestimate of the actual concentrations of Rotigotine that are likely to be present in the environment.

Additional Data

Ready biodegradation

A ready biodegradation test, following OECD 301B (modified sturm test), demonstrated that Rotigotine is not readily biodegradable under the conditions of the test. A separate activated sludge respiration inhibition test (OECD 209) was conducted and the EC_{50} for Rotigotine determined to be 1825 mg/L (Section 5.1.4). Rotigotine is, therefore, not considered to have an adverse effect on activated sludge and inhibition can be ruled out as a reason for the lack of biodegradation in the ready biodegradation test.

Degradation in Water-Sediment systems

The degradation of [^{14}C]-Rotigotine in two natural water-sediment systems, under aerobic and anaerobic conditions, was studied at 20 ± 2°C in the dark. The study was conducted in accordance with OECD guideline 308. Rotigotine dissipated from the surface water into the sediment with DT50 values of 2 to 3 days under aerobic conditions. The DT50 of Rotigotine in natural water-sediment systems, under aerobic conditions, in the dark, at 20 ± 2°C, was in the range 20 to 157 days. Under anaerobic conditions, the same processes occurred at a much slower rate.

Bioaccumulation

The distribution coefficients of Rotigotine were determined by the shake flask method using different buffer systems and octanol. The principles of the OECD guideline 107, Partition Coefficient (n-octanol/water): Shake Flask Method were considered. The low logD value at pH 4.5 is indicative that the compound is partly eliminated by urine. At environmentally relevant pH, (6 to 8) it is likely that the logD (log K_{ow}) would exceed 3 (K_{ow} > 1000).

This indicates that there may be a tendency for Rotigotine to transfer from the aquatic environment into organisms with a potential to bioaccumulate. As a result, a Tier B fish bioconcentration study was performed in order to investigate the potential of Rotigotine to bioaccumulate following the methods detailed in OECD guideline 305.

The BCF and degradation rate indicate that Rotigotine is unlikely to bioaccumulate to any significant extent in fish tissues. In addition, the removal of Rotigotine from surface water bodies is rapid as demonstrated in the water-sediment study thus limiting the exposure of the fish.