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# Environmental Risk Assessment
## VIMPAT®

## Summary

Lacosamide is not readily biodegradable.

The PEC:PNEC ratios indicate that lacosamide is unlikely to be a concern for the aquatic environment and the risk is classified at an insignificant level

Lacosamide is not expected to bioaccumulate to any significant extent (Kow <1000).

## PEC – Predicted Environmental Concentration

PEC= 0,0057 mg/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 (600 mg),
- FPEN: Market penetration factor (see below)
- WASTEWINH: Amount (litres) of wastewater per inhabitant per day (Default = 200 L*inh-1*d-1)
- Dilution: Dilution factor (Default = 10)

Assuming that lacosamide is the only drug used for epilepsy treatment, the refined FPEN was estimated as follows:

$$F_{PEN} = P_{REGION} \times \frac{T_{TREATMENT} \times n_{TREATMENT,P}}{N_D}$$

Where,

- FPEN: Market penetration factor,
- PREGION: Prevalence in the region (average – estimated 0,019 in a worst case scenario),
- TTREATMENT: Duration of one treatment period (assumed to be 365 days/year for a conservative estimate),
- nTREATMENT,P: Number of treatment periods per year (since the treatment is assumed to continue throughout the year, this is considered to be 1),
- ND: Number of days per year

FPEN = 0.019 x 365 x 1/365 = 0.019 (1.9%)

## PNEC – Predicted No-Effect Concentration

PNEC > 1 mg/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 PNEC is derived from the lowest NOEC (No Observed Effect Concentration) measured. For Lacosamide, no effects on the biological parameters tested (on Brachydanio rerio early life stage) were observed up to the highest test concentration (LOEC > 10 mg/L). Consequently, the NOEC was ≥ 10 mg/L. This value was used for the risk assessment since it was the nominal lowest endpoint.

The NOEC might be even higher, but concentrations above nominal 10 mg/L are not to be tested according to the guideline. The NOEC is divided by 10 as per EMA guidelines to obtain a PNEC > 1 mg/L.

## Environmental Risk Level – PEC/PNEC ratio

PEC/PNEC = 0,0057/1 = 0,0057

The PEC/PNEC ratio is below 0,1. The proposed use of lacosamide is therefore considered unlikely to represent an unacceptable risk to water and the risk is classified at an insignificant level.

# Additional Data

The physico-chemical characterization of lacosamide (water solubility of > 20 g/L, Henry Law Constant of 1.14 * 10-11 atm*m3 /mol, log Kow of 0.25, no relevant dissociation at environmentally relevant pH) indicate the substance to be predominantly present in the water phase in undissociated form in the aquatic environment. The potential for bioconcentration is therefore considered to be low (log Kow < 3) , and no further testing on bioconcentration or chronic aquatic toxicity is indicated according to the testing procedures of the EU TGD.

Physico-chemical data on the major human metabolite SPM 12809 (O-desmethyl lacosamide) are not available. But concluding from its chemical structure and the retention times in HPLCruns the substance is considered more polar than lacosamide, and therefore expected to have a comparable or higher water solubility than the parent compound.

According to the respective OECD Guidelines (Modified Sturm test, OECD 301 B), based on ultimate biodegradation (i.e. CO2 evolution), lacosamide has to be considered to be not ready biodegradable under the test conditions.