

Metadon Nordic Drugs



Nordic Drugs

Oral lösning 100 mg

(Klar, färglös lösning med lukt och smak av hallon.)

 Narkotikaklass: II - Narkotika med medicinsk användning

Särskilt läkemedel

Medel vid opioidberoende

Aktiv substans:

Metadon

ATC-kod:

N07BC02

Läkemedel från Nordic Drugs omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Metadon

Miljörisk: Användning av metadon har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Metadon är potentiellt persistent.

Bioackumulering: Metadon har låg potential att bioackumuleras.

Detaljerad miljöinformation

METADON NORDIC DRUGS (Methadone hydrochloride)

Summary

Environmental risk:

- Use of Methadone hydrochloride has been considered to result in insignificant environmental risk.
- Användning av Metadonhydroklorid har bedömts medföra försumbar risk för miljöpåverkan.

Degradation:

- Methadone hydrochloride is potentially persistent.
- Metadonhydroklorid är potentiellt persistent.

Bioaccumulation:

- Methadone hydrochloride has low potential for bioaccumulation.
- Metadonhydroklorid har låg potential att bioackumuleras.

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$PEC (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

$$PEC = 0.0132 \mu\text{g/L}$$

Where:

A = 96,49 kg (total sold amount API in Sweden year 2020, data from IQVIA).

R = 0 % removal rate. This is considered a conservative value.

P = number of inhabitants in Sweden = $10 \cdot 10^6$ ¹

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. 1)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. 1)

Predicted No Effect Concentration (PNEC)

Calculation of PNEC is obtained by applying assessment factors (AF) to long-term ecotoxicity data:²

Lowest NOEC/AF

$$PNEC = 3.8 \mu\text{g/L}$$

Where:

Lowest NOEC = 0,19 mg/L (*Daphnia magna*, reproduction, chronic toxicity).

AF = 50 based on the availability of chronic toxicity studies for two trophic levels.

¹ According to *Environmental classification of pharmaceuticals* www.fass.se. *Guidance for pharmaceutical companies* (2012 v 3.0)

² Guidance on information requirements and chemical safety assessment Chapter R10 (ECHA, 2008)

Ecotoxicological studies

Algae (Pseudokirchneriella subcapitata) (OECD 201) (Ref. 2):

NOEC 72 h (growth inhibition) = 0.31 mg/L

Crustacean (Daphnia magna):

Acute toxicity (OECD 202) (Ref. 3)

EC₅₀ 24 h (immobilization) = 22 mg/L

EC₅₀ 48 h (immobilization) = 15 mg/L

NOEC 24 h (immobilization) = 3.8 mg/L

NOEC 48 h (immobilization) = 1.9 mg/L

Chronic toxicity (OECD 211) (Ref. 4)

NOEC 21 d (reproduction) = 0.19 mg/L

Fish (Brachydanio rerio):

Acute toxicity (OECD 203) (Ref. 5)

LC₅₀ 96 h = 28 mg/L

NOEC 96 h = 10 mg/L

Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 0.0132/3.8 = 0.00347$, i.e. $PEC/PNEC \leq 0.1$ which justifies the phrase "Use of METADON NORDIC DRUGS (Methadone hydrochloride) has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:

In an aerobic biodegradation study (28 days) in water (according to OECD Guideline 301 A) Methadone hydrochloride was not considered as readily biodegradable (Ref. 6).

Inherent degradability:

No data on inherent degradability.

Simulation studies:

No data on simulation studies.

Abiotic degradation

Hydrolysis: No data on hydrolysis.

Photolysis: No data on photolysis.

Justification of chosen degradation phrase:

Methadone hydrochloride did not pass the ready biodegradation test (OECD Guideline 301 A) and there is no data on mineralisation. The phrase "Methadone hydrochloride is potentially persistent" is thus chosen.

Bioaccumulation

Bioconcentration factor (BCF):

The $\log K_{ow}$ (2.07) indicates little potential for bioconcentration in aquatic species. Therefore, based on the low $\log Kow$ value, a bioconcentration study was not considered to be required.

Partitioning coefficient:

The octanol/water partition coefficient of methadone hydrochloride at pH 7.4 is 117. $\log K_{ow}$ is 2.07 (Ref. 7).

Justification of chosen bioaccumulation phrase:

Since $\log K_{ow} < 4$ at pH 7.4, methadone hydrochloride has low potential for bioaccumulation.

Excretion (metabolism)

Methadone hydrochloride undergoes N-demethylation to the main metabolites

2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP). Neither metabolite is pharmacologically active. The metabolites are excreted in the urine and the bile along with small amounts of other metabolites and unchanged drug (Ref. 8). Due to uncertainty about the amounts excreted, worst case (i.e. 100% is excreted as the active parent molecule) is used in the PEC calculation.

PBT/vPvB assessment

Methadone hydrochloride does not meet all three properties that are required in order to classify a compound as PBT and is considered not to fulfil the criteria for PBT or vPvB.

References

1. ECHA, European Chemicals Agency. 2016 Guidance on information requirements and chemical safety assessment. Chapter R.16: Environmental exposure assessment. Version 3.0 (February 2016)
Information_requirements_r16
2. Toxicon (2009). Freshwater alga and cyanobacteria, Growth Inhibition Test (OECD 201). Report 021/09.
3. Toxicon (2009). Daphnia sp., Acute Immobilisation Test (OECD 202). Report 022/09.
4. Toxicon (2009). Daphnia magna, Reproduction Test (OECD 211). Report 023/09.
5. Toxicon (2009). Fish, Acute Toxicity Test (OECD 203). Report 023/09.
6. AnoxKaldnes AB (2009). Evaluation of the aerobic biodegradability of Methadoni hydrochloridum Eur (OECD 301 A). Report 09-101.
7. RxList (2009). RxList_methadone-hydrochloride
8. Metadon Nordic Drugs: Summary of Product Characteristics (SPC)