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MRF

Otsuka Pharma Scandinavia

Pulver och vätska till injektionsvätska, depotsuspension 400 mg
(pulver: vitt till benvitt; vätska: klar)

Antipsykotikum

Aktiv substans:
Aripiprazol (vattenfri)

ATC-kod:
N05AX12

Läkemedel från Otsuka Pharma Scandinavia omfattas av Läkemedelsförsäkringen.
Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Aripiprazol (vattenfri)

Miljörisk: Användning av aripiprazol har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Aripiprazol bryts ned långsamt i miljön.
Bioackumulering: Aripiprazol har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A$ (100-R)

PEC = 0.01025 µg/L

Where:

A = 74.79517 kg (total sold amount API in Sweden year 2022, data from IQVIA).

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

P = number of inhabitants in Sweden = $10*10^{6}$

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:

Lowest NOEC/AF

PNEC = 0.261 µg/L

Where:

Lowest NOEC = 0.00261 mg/L (*Daphnia magna*, reproduction, chronic toxicity)

AF = 10 based on the availability of chronic toxicity studies for three trophic levels

Ecotoxicological studies

Algae (*Pseudokirchneriella subcapitata)* (OECD 201) (Ref. 2):
ErC50 72h (growth rate) > 0.14 mg/L (no effects were noted at the limit of solubility in the algal medium)
NOEC (growth rate) = 0.14 mg/L
EbC50 72 h (biomass) > 0.14 mg/L
NOEC (biomass) = 0.14 mg/L

Crustacean (Daphnia magna):
Acute toxicity (OECD 202) (Ref. 3)
EC50 48 h > 0.031 mg/L (no effects were noted at the limit of solubility in the system)
NOEC 48 h = 0.031 mg/L

Chronic toxicity (OECD 211) (Ref. 4)
NOEC 21 d (growth) = 0.0781 mg/L
LOEC 21 d (growth) = 0.228 mg/L
NOEC 21 d (reproduction) = 0.00261 mg/L
LOEC 21 d (reproduction) = 0.00731 mg/L

Fish (Onchorhymchus mykiss):
Acute toxicity (OECD 203) (Ref. 5)
LC50 96 h > 0.12 mg/L (mortality was not observed at the limit of solubility in the system)
NOEC 96 h = 0.047 mg/L (darkened pigmentation observed at ≥ 0.1 mg/L)

Fish (Pimephales promelas):
Chronic toxicity (OECD 210) (Ref. 6)
NOEC 28 d (hatching success) = 0.213 mg/L

NOEC 28 d (survival) = 0.0058 mg/L
NOEC 28 d (growth) = 0.0136 mg/L

Other ecotoxicity data:
Activated Sludge Respiration Inhibition (OECD 209) (Ref. 7)
EC50 > 1000 mg/L (highest dose)
EC10 ≈ 100 mg/L (10.3% inhibition at 100 mg/L, 8.59% inhibition at 1000 mg/L)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.01025/0.261 = 0.03926, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of aripiprazole has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:
In an aerobic biodegradation study in water (according to FDA Guideline 3.11) [^{14}C]Aripiprazole was not readily biodegraded. There was negligible mineralization to CO_2 (0.034% over 42 days). Some primary degradation occurred (approximately 10% by day 38). (Ref. 8)

Inherent degradability:
No data on inherent degradability.

Simulation studies:
The fate of aripiprazole was studied in two aquatic sediment systems (according to OECD Guideline 308). Aripiprazole declined

in the water phase over time and increased in the sediment. DT50 values for aripiprazole (total system) were 30.9 and 177 days for the two sediments (higher vs. lower organic carbon content). Several metabolites of aripiprazole were formed, including OPC-14857 and M1. Bound residues increased over time to approximately 30% of administered radioactivity. (Ref. 9)

Based on the two DT50 values, aripiprazole is considered to be slowly degraded in the environment.

Abiotic degradation

Hydrolysis: No data on hydrolysis
Photolysis: No data on photolysis.

Justification of chosen degradation phrase:

Aripiprazole did not pass the ready degradation test (FDA Guideline 3.11) and was slowly degraded in the environment in a simulation study in two aquatic sediment systems (OECD Guideline 308). Data on abiotic degradation is lacking. Based on these data aripiprazole is considered “slowly degraded in the environment”.

Bioaccumulation

Bioconcentration factor (BCF):
The Log Kow (< 3) 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. The estimated BCF is 53.9 – 85.7 (Ref 10).

Partitioning coefficient:

Log K_{ow} for [^{14}C]Aripiprazole was determined according to FDA Guideline 3.02. The partitioning coefficient is dependent upon pH

and Log K_{ow} at 25 °C is 2.7 at pH 5; 2.95 at pH 7 and 2.89 at pH 9 (Ref 10). Log D_{ow} will be < 4 at pH 7.

Determination of sorption/desorption properties
In a screening sorption/desorption study in sludge (according to FDA Guideline 3.08), Koc was 10270 in purified water and 2850 in 0.01M $CaCl_2$; % sorbed was 67 – 88. (Ref. 11) In another study (according to OECD Guideline 106), K_{Foc} ranged from 10900 to 106000 when incubated in 0.01 $CaCl_2$. (Ref. 12)

The sorption/desorption study results indicate that aripiprazole has high affinity for organic carbon in activated sludge. During wastewater treatment, sorption to sludge will act as a depletion mechanism from water.

Justification of chosen bioaccumulation phrase:
Since estimated BCF <500 and log D_{ow} < 4 at pH 7, aripiprazole is considered to have “low potential for bioaccumulation”.

Excretion (metabolism)
Approximately 76% of the administered dose of aripiprazole is excreted via urine and primarily faeces. The material excreted consists primarily of parent compound and three inactive metabolites that each is excreted at greater than 10% of the patient dose; and in addition to the three inactive metabolites, one known active metabolite at 3.3%. (Ref. 13) Only the metabolite present at 3.3% is pharmacologically active and similar in activity to aripiprazole.

PBT/vPvB assessment

Aripiprazole 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) https://echa.europa.eu/guidance-documents/guidance-on-informat .
2. Hoberg, J. 2001. Aripiprazole - Toxicity to the Freshwater Green Alga, *Pseudokirchneriella subcapita*. Springborn Smithers Laboratories, Inc., Study No. 12534.6210.
3. Machado, M. 2001. Aripiprazole - Acute Toxicity to Daphnids (*Daphnia magna*) under Static Conditions. OECD 202, Springborn Smithers Laboratories, Inc., Study No. 12534.6211.
4. Burke, J., 2008. Aripiprazole Prolonged Toxicity to *Daphnia magna*, Huntingdon Life Sciences Report No. BMY 1242.
5. Machado, M. 2001. Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) under Static Conditions. Springborn Smithers Laboratories, Inc., Study No. 12534.6212.
6. Burke, J., 2008. Aripiprazole Fish Early Life Stage Toxicity Test for Fathead Minnow, Huntingdon Life Sciences Report No. BMY 1243.
7. McLaughlin, S., 2001, Aripiprazole - Determination of Activated Sludge Respiration Inhibition, Springborn Smithers Laboratories, Inc., Study No. 12534.6213.

8. McLaughlin, S.P. 2001. [^{14}C]Aripiprazole - Determination of Aerobic Biodegradation in Water. Springborn Smithers Laboratories, Inc., Study No. 12534.6209.
9. Crowe, A., 2008. Aripiprazole - Aerobic Metabolism in Aquatic Sediment Systems, Huntingdon Life Sciences Report No. BMY 1244.
10. Sulaiman, M.W., 2001. [^{14}C]Aripiprazole - Determination of the n-Octanol/Water Partition Coefficient. Springborn Smithers Laboratories, Inc., Study No. 12534.6214.
11. McLaughlin, S.P. 2001. [^{14}C]Aripiprazole - Determination of the Sorption and Desorption Properties. Springborn Smithers Laboratories, Inc., Study No. 12534.6215.
12. Kane, T., 2008. Aripiprazole - Adsorption/Desorption on Soils and Sewage Sludge, Huntingdon Life Sciences Report No. BMY 1245.
13. Leese, P, 2001. A Study of the Absorption, Distribution, Metabolism and Excretion Following Oral Administration of ^{14}C-OPC-14597 in Health Volunteers. BristolMyers Squibb Pharmaceutical Research Institute. Accession No. 920011356.