FASS

Mirtazapin Bluefish

Bluefish Pharma

Munsönderfallande tablett 15 mg

(Vita, runda munsönderfallande tabletter präglade med 36 på den ena sidan och A på den andra sidan med en upphöjd, rund kant. 6,5 x 6,5 mm.)

Övriga antidepressiva medel

Aktiv substans:

Mirtazapin

ATC-kod:

N06AX11

Läkemedel från Bluefish Pharma omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för mirtazapin är framtagen av företaget MSD för Remeron®, Remeron®-S

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

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$PEC\ (\mu g/L) = (A*10^{9}*(100-R))/(365*P*V*D*100) = 1.5*10^{-6}*A(100-R)$

PEC = 0.17 µg/L

Where:

A = 1165 kg (total sold amount API in Sweden year 2015, data from IMS Health).
R = 0 % removal rate (worst case assumption)
P = number of inhabitants in Sweden = $9 * 10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. I)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Algae (Pseudokirchneriella subcapitata) (*OECD 201) (Reference XII):
NOEC (72 hr) (growth rate) = 1200 µg/L

Algae (Selenastrum capricornutum) (USFDA 4.01) (Reference II):
NOEC (14 day) (cell number) = 9700 µg/L
MIC = 19500 µg/L

Algae (Microcystic aeruginosa) (USFDA 4.01) (Reference II):
NOEC (21 day) (cell number) = 4900 µg/L
MIC = 9700 µg/L

Crustacean, water flea (Daphnia magna):
Acute toxicity
EC_{50} 48 h (mortality) = 19500 µg/L (USFDA 4.09) (Ref. III)

Chronic toxicity
NOEC (21 day) (reproduction and growth) = 320 µg/L (OECD 211) (Ref. IV)

Fish, fathead minnow (Pimephales promelas):
Acute toxicity
EC_{50} 96 h (mortality) = 6920 µg/L (USFDA 4.11) (Ref. V)

Chronic toxicity
NOEC (31 day) (larval survival) = 360 µg/L (OECD 210) (Ref. VI)

PNEC = 32 µg/L (320 µg/L/ 10 based on the most sensitive NOEC for the daphnia and an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = .17/32 = 0.005, i.e. PEC/PNEC ≤ .1 which justifies the phrase "Use of mirtazapine has been considered to result in insignificant environmental risk".

Biotic degradation

Biodegradation Simulation Screening
Test results 4% degradation in 28 days in water (US FDA 3.11) (Ref. VII)

Biodegradation Simulation Screening
Test results 1% degradation in 28 days in sediment (US FDA 3.11) (Ref. VIII)

Sediment Transformation (OECD 308) (Ref. IX)

Half-life = 55 days in total water-sediment systems
Half-life = 6 - 7.5 days in water layer

At each sampling interval, samples from each test system were separated into water and sediment phases. The sediment was extracted once with acetonitrile: trifluoroacetic acid 99:1.0 (v:v) and once with acetonitrile:purified reagent water:trifluoroacetic acid 80:20:1.0 (v:v:v). The sediment, with the exception of the Day 0 samples, was then extracted again with acetonitrile:purified reagent water:trifluoroacetic acid 80:20:1.0 (v:v:v) for a maximum of three extractions. The water and sediment extracts were radioassayed by liquid scintillation counting (LSC) and then analyzed by high performance liquid chromatography with radiochemical detection (HPLC/RAM) to quantify [^{14}C]ORG 3770 and any degradation products in each phase. Radioactivity in the extracted solids (sediment bound) was quantified by combustion analysis with LSC and the liquid traps for volatile gases were radioassayed by LSC.

Evidence of primary degradation was observed for [^{14}C]ORG 3770 in samples from both aerobic water/sediment test systems. One major region (> 10% AR) of radioactivity was observed in the chromatograms for the Weweantic River samples (metabolite identified as Met #4). Several minor regions of radioactivity were observed in some chromatograms for the Taunton River and Weweantic River (including metabolites identified as Met #1, #2, #3 and #5 as well as “Others”). In all cases, the peak averages each represented < 10% AR and Met #1, #2 and #5, and “Others” were not considered further. However, Met #3 (approached 10% AR) and #4 (> 10% AR) were further characterized by LC-MS.

Average material balance (as percent of applied radioactivity) ranged from 92.9 to 97.8% AR for the Taunton River throughout the 100-day study. Average material balance ranged from 93.4 to 98.2% AR for the Weweantic River throughout the 100-day study.
Ultimate biodegradation was observed in the aerobic test systems to be minimal. The cumulative amount of evolved $^{14}CO_2$ was 0.2% AR for the Taunton River and Weweantic River aerobic test systems at Day 100. The cumulative amounts of volatile organics were < 0.1% AR for the Taunton River and Weweantic River aerobic test systems at Day 100.

Abiotic degradation

Photolysis:
Half-life = 0.35 hours at pH 7 (US FDA 3.10) (Ref. X)

Justification of chosen degradation phrase:
Mirtazapine does not pass the ready biodegradation test but is inherently degradable in acclimated biological systems. The DT_{50} ≤ 120 d for the total system, therefore the phrase “Mirtazapine is slowly degraded in the environment” was chosen.

Bioaccumulation

Bioconcentration Factor:
Steady State BCF = 201 to 239 (OECD 305). (Ref. XI)

Justification of chosen bioaccumulation phrase:
Since BCF < 500, the substance has low potential for bioaccumulation.

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.

http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

II. Akzo Research, 1993. Effect of Mirtazapine on the Growth Rate and Standing Crop of Two Algal Species.

III. Akzo Research, 1993. Acute Toxicity of Mirtazapine to Daphnia magna.

IV. NOTOX B.V., 2012. Daphnia magna Reproduction Test with Org 3770 (Semi Static).

V. Akzo Research, 1993. Acute Toxicity of Mirtazapine to Pimephales promelas.

VI. NOTOX B.V., 2012. Fish Early Life Stage Toxicity Test with Org 3770 (Semi Static).

VII. Akzo Research, 1993. Aerobic Biodegradation of Mirtazapine in Water.

VIII. Akzo Research, 1993. Aerobic Biodegradation of Mirtazapine in Sediment.

IX. Smithers Viscient, 2012. [14C]Org 3770: Aerobic Transformation in Aquatic Sediment Systems Based on OECD Guideline 308.

X. Akzo Research, 1993. Aquatic Photodegradation of Mirtazapine.

XI. NOTOX B.V., 2012. Bioconcentration Test in Bluegill with ORG 3770 (Flow-Through).

XII. Smithers Viscient, 2014. ORG 3770: 72-hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline 201.