FASS

Malarone® Junior

GlaxoSmithKline

Filmdragerad tablett 62,5 mg/ 25 mg
(rund, bikonvex, rosa, 7,5 x 7,5 mm, utan skåra ,märkt "GX CG7")

Malariamedel

Aktiva substanser:
Atovakvon
Proguanil

ATC-kod:
P01BB51

Läkemedel från GlaxoSmithKline omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Atovakvon

Miljörisk: Risk för miljöpåverkan av atovakvon kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.
Nedbrytning: Det kan inte uteslutas att atovakvon är persistent, då data saknas.
Bioackumulering: Atovakvon har hög potential att bioackumuleras.

Detaljerad miljöinformation

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

PEC = 0.035 µg/L

Where:
A = 235.41 kg (total sold amount API in Sweden year 2014, data from IMS Health).

R = 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation).

P = number of inhabitants in Sweden = $9 * 10^6$

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

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

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae:
No data

Water flea (Daphnia magna):
Acute toxicity
EC50 48 h (immobility) = 3.50 µg/L (OECD 202) (Reference 3)

Water flea (Ceriodaphnia dubia):
Chronic toxicity
NOEC 8 days (reproduction) = 0.083 µg/L (USEPA 1002) (Reference 9)

Fish
Acute toxicity
No data

Chronic toxicity
No data

Other ecotoxicity data:
Microbial Inhibition Concentration (Reference 5)
MIC > 11 µg/l, Aspergillus flavus
MIC > 11 µg/l, Azotobacter chroococcum
MIC > 11 µg/l, Chaetomium globosum
MIC > 11 µg/l, Nostoc sp.
MIC > 11 µg/l, Pseudomonas acidovorans

Earthworm (*Eisenia foetida*):
NOEC 14 days (lethality) = 1000 mg/kg (OECD 207) (Reference 4)

PNEC cannot be calculated because data is not available for all three (algae, crustacean and fish) of the toxicity endpoints.

Environmental risk classification (PEC/PNEC ratio)

Risk of environmental impact of atovaquone cannot be excluded, since there is not sufficient ecotoxicity data available.

Degradation

Biotic degradation

Ready degradability:
No data

Inherent degradability:
No Data

Soil Metabolism:
50% degradation in < 1 day (OECD 307) (Reference 6)

Abiotic degradation

Hydrolysis:
No data

Photolysis:
50 % degradation in 2.63 h (TAD3.10). (Reference 8)

STP Removal

Soil-sediment Sorption log Koc = 4.15 – 4.58 (Reference 7)

Atovaquone is predicted to strongly sorb to organic matrices such as soil, sediment and sludge. Therefore, this substance is likely to be significantly removed from the aquatic environment via sorption to sludge solids. It is anticipated that atovaquone will reach the terrestrial environment via the spreading of sludge solids on agricultural land. EUSES (SimpleTreat) modelling predicts that 78.40% of this substance will distribute to sludge (Reference 3). This is consistent with ADME observation that 94% of the drug substance dose is found in faeces (Reference 2) and not urine. Approximately, 21% of atovaquone will enter the aquatic environment where significant binding to water sediments is expected.

Justification of chosen degradation phrase:

Atovaquone is rapidly degraded in soil, the compartment to which it is likely to partition. For the terrestrial compartment the phrase ‘atovaquone is degraded in the environment’ is appropriate. However, for the aquatic compartment the phrase “The potential for persistence of Atovaquone cannot be excluded, due to lack of data” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Log Kow = 5.31 at pH 7 (TAD 3.02). (Reference 10)

Justification of chosen bioaccumulation phrase:
Since log Kow > 4 at pH 7, the substance has a high potential for bioaccumulation.

Excretion (metabolism)

Greater than 94% of the dose was recovered as unchanged atovaquone in the feces over 21 days. There was little or no excretion of atovaquone in the urine (less than 0.6%). There is indirect evidence that atovaquone may undergo limited metabolism; however, a specific metabolite has not been identified. (Reference 2)

PBT/vPvB assessment

The appropriate degradation data are not available to assign PBT/vPvB criteria.

Please, also see Safety data sheets on http://www.msds-gsk.com/ExtMSDSlist.asp.

References

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

2. Product Information Mepron. Prescribing information GlaxoSmithKline, Research Triangle Park, NC, May 2008.

3. http://www.rivm.nl/rvs/Risicobeoordeling/Modellen_voor_risicobeoordeling/EUSES

4. Sewell IG and Bartlett AJ. 566C80: Acute Toxicity to Daphnia magna. Report No. 303/786. Safepharm Laboratories Limited, June 1997.

5. Wetton PM. Atovaquone: Acute Toxicity to Earthworms (Eisenia foetida). Report No. 1127/299. Safepharm Laboratories Limited, July 2004.

6. Hopkins BT. Microbial Inhibition with 566C80. Report No. 40173. ABC Laboratories Limited, September 1992.

7. Roulstone P and Mckenzie J. Atovaquone: Aerobic Biodegradation in Soil. Report No. 1127/302. Safepharm Laboratories Limited, November 2004.

8. Gorman M and Abney BS. Soil-Sediment Adsorption-Desorption of 566C80. Report No. 40174. ABC Laboratories Limited, September 1992.

9. Gorman M and Pratt M. Determination of the Aqueous Photodegradatio of 14C 566C80. Report No. 40175. ABC Laboratories Limited, September 1992.

10. Goodband TJ and Mullee DM. Atovaquone: Daphnid, Ceriodaphnia Dubia Survival and Reproduction Test. Report No. 1127/1774. Harlan Laboratories Limited, September 2010.

11. Material Safety Data Sheet for Malarone® Tablets. SDS number 123528. GlaxoSmithKline plc, July 2008.

Proguanil

Miljörisk: Användning av proguanil har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Proguanil är potentiellt persistent.
Bioackumulering: Proguanil har låg potential att bioackumuleras.

Detaljerad miljöinformation

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)
PEC is calculated according to the following formula:

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

PEC = 0.013 µg/L

Where:
A = 88.84 kg (total sold amount API in Sweden year 2014, data from IMS Health).
R = 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation).

P = number of inhabitants in Sweden = $9 *10^{6}$

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

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

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Selenastrum capricornutum):
EC50 72 h (growth rate) = 730 µg/L (OECD 201) (Reference 4)
NOEC = 250 µg/L

Water flea (Daphnia magna):
Acute toxicity
EC50 48 h (immobility) = 16,400 µg/L (OECD 202) (Reference 3)

Water flea (Ceriodaphnia dubia):
Chronic toxicity
NOEC 8 days (reproduction) = 5,600 µg/L (USEPA 1002) (Reference 5)

Rainbow trout (Oncorhyncus mykiss):
Acute toxicity
LC50 48 h (lethality) = 100,000 µg/L (OECD 203) (Reference 7)
Chronic toxicity
No data

Other ecotoxicity data:
Microorganisms in activated sludge:
EC50 3 h (inhibition) = 39,800 µg/L (OECD 209) (Reference 3)

PNEC = 250/50 = 5 µg/L
PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for green alga (= 250 ug/L) has been used for this calculation since it is the most sensitive of the three tested species.

Environmental risk classification (PEC/PNEC ratio)
PEC/PNEC = 0.013/5= 0.0026, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of proguanil has been considered to result in insignificant environmental risk.”

Degradation
Biotic degradation
Ready degradability:
4.03% degradation in 28 days (TAD 3.11) (Reference 3)

Inherent degradability:
< 4% degradation in 28 days (OECD 302B) (Reference 6)

Abiotic degradation
Hydrolysis:
No data

Photolysis:

Justification of chosen degradation phrase:
Proguanil is not readily degradable or inherently degradable. The phrase “proguanil is potentially persistent in the environment” is thus chosen.

Bioaccumulation
Partitioning coefficient:
Log Dow = 0.99 at pH 7 (TAD 3.02). (Reference 3)

Log Dow at pH 5 = 0.99
Log Dow at pH 7 = 0.99
Log Dow at pH 9 = 1.56

Justification of chosen bioaccumulation phrase:
Since log Dow < 4 at pH 7, the substance has low potential for bioaccumulation.

Excretion (metabolism)
Between 40% to 60% of proguanil is excreted by the kidneys. Proguanil is metabolized to cycloguanil (primarily via CYP2C19) and 4-chlorophenylbiguanide. The main routes of elimination are hepatic biotransformation and renal excretion. (Reference 2)

PBT/vPvB assessment
Proguanil does not fulfil the criteria for PBT and/or vBvP.

All three properties, i.e. ‘P’, ‘B’ and ‘T’ are required in order to classify a compound as PBT (Reference 1). Proguanil does not fulfil the criteria for PBT and/or vBvP based on log Pow < 4.

Please, also see Safety data sheets on http://www.msds-gsk.com/ExtMSDSlist.asp.

References

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

2. Product Information: Malarone Prescibing Information. GlaxoSmithKline, Research Triangle Park, NC, June 2008.
3. Proguanil hydrochloride; Environmental Fate and Effects Tests. Report no. K21784. ABC Laboratories, April 1998.

4. Shillabeer N, Smyth DV and Kent SJ. Proguanil hydrochloride: Toxicity to Green Alga Selenastrum capricornutum. Report No. BL7677/B. Brixham Environmental Laboratories, July 2004.

5. Young BE and Kent SJ. Proguanil hydrochloride: Determination of the 3 brood (7 day)chronic toxicity to Ceriodaphnia dubia. Report No. BL8266/B. Brixham Environmental Laboratories, April 2006.

6. Shillabeer N and Magor SE. Proguanil hydrochloride: Determination of Inherent Biodegradability (Zahn-Wellens Test). Report No. BL7678/B. Brixham Environmental Laboratories, June 2004.

7. Material Safety Data Sheet for Malarone® Tablets. SDS number 123528. GlaxoSmithKline plc, July 2008.