FASS

Combivir®

GlaxoSmithKline

Filmdragerad tablett 150 mg/ 300 mg
(Vit till off-white, kapselformad, 7,3 x 17,7 mm, filmdragerad tablett med brytskåra och med koden "GXFC3" på båda sidorna)

Virushämmande medel mot hivinfektioner, kombinationer

Aktiva substanser (i bokstavsordning):
Lamivudin
Zidovudin

ATC-kod:
J05AR01

Läkemedel från GlaxoSmithKline omfattas av Läkemedelsförsäkringen.
Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Lamivudin

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

Nedbrytning: Lamivudin bryts ned i miljön.
Bioackumulering: Lamivudin 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 = 0.028 µg/L

Where:
A = 205.36 kg (total sold amount API in Sweden year 2020, data from IQVIA).
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 = $10*10^{6}$
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

Green Algae (Selenastrum caprocornutum):
IC50 72h (growth) > 96,900 µg/L (OECD 201) (Reference 7)
NOEC > 96,900 µg/L

Water flea (Daphnia magna):
Acute toxicity
EC50 48 h (immobility) > 1,000,000 µg/L (OECD 202) (Reference 5)
NOEC > 1,000,000 µg/L

Water flea (Ceriodaphnia dubia):
Chronic toxicity
EC50 7 days (reproduction) > 100,000 µg/L (EPA 1002) (Reference 10)
NOEC = 100,000 µg/L

Water flea (Daphnia magna):
Chronic toxicity
EC50 21 days (reproduction) > 100,000 µg/L (OECD 211) (Reference 12)
NOEC = 100,000 µg/L

Rainbow Trout (Juvenilee Oncorhyncus mykiss):
Acute toxicity
LC50 96 h (lethality) > 97,700 µg/L (OECD 203) (Reference 8)
NOEC = 97,700 µg/L

Fathead Minnow (Pimephales promelas):
Chronic toxicity
LC50 96 h (lethality) > 10,000 µg/L (OECD 210) (Reference 13)
NOEC = 10,000 µg/L

Other ecotoxicity data:
Microorganisms in activated sludge

EC50 3 hours (Inhibition) > 1,000,000 µg/L (OECD 209) (Reference 11)
NOEC = 1,000,000 µg/L

Chironomid (Chironomus riparius)
NOEC 28 days (development) = 100,000 µg/kg (OECD 218) (Reference 14)

PNEC = 10,000/10 = 1,000 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fish (= 10,000 ug/L) has been used for this calculation since it represents the lowest value for all three tested species.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.028/1,000 = 2.80 x 10^{-5}, i.e. PEC/PNEC ≤ 1 which justifies the phrase “Use of lamivudine has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:
< 1% degradation in 28 days (OECD 301B) (Reference 4)

Inherent degradability:
0% degradation in 28 days (OECD 302B) (Reference 9)
4% primary (loss of parent) degradation in 28 days

15-24% degradion in soil (TAD 3.12) (Reference 3)

Simulation studies:

Water-sediment study:

50% (DT_{50}) decline (total system) = 22-29 days (OECD 308)

(Reference 14)

Total Lamivudine (day 100) = 0.4% - 0.6%

CO_2 = 8.50% - 12.60%

Total Non-extractable residue = (day 100) = 18.60% - 19.10%

Extraction methods: The non-extractable radioactivity in the samples taken at 100 days was characterised using an acid/base fractionation procedure. Sediment debris was extracted with 0.5 M sodium hydroxide by shaking on an orbital shaker overnight at ambient temperature. The debris was separated by centrifugation and the supernatant removed. The debris was washed with 0.5 M sodium hydroxide and allowed to air-dry. The supernatant was adjusted to pH 1 with concentrated hydrochloric acid and left to stand at ambient temperature. The sample was centrifuged, the precipitate washed with 1 M HCl and the supernatant combined with these washings. The volume of this solution, the fulvic acid fraction, was measured and duplicate aliquots taken for radio-assay. The precipitate, the humic acid fraction, was dissolved in 0.5 M sodium hydroxide.

Abiotic degradation

Hydrolysis:

Half-life, pH 7 > 1 year (OECD 111) (Reference 4)

Photolysis:

No data

Justification of chosen degradation phrase:

Lamivudine is not readily biodegradable nor inherently biodegradable.
Lamivudine DT50 < 32 days and the presence of the parent is < 15%.
The phrase “Lamivudine is degraded in the environment” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Log Dow = -1.44 at pH7. (TAD 3.02) (Reference 3)

Log Dow at pH5 = -1.17
Log Dow at pH7 = -1.44
Log Dow at pH9 = -1.86

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

Excretion (metabolism)

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding. (Reference 2)

PBT/vPvB assessment

Lamivudine 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). Lamivudine does not fulfil the criteria for PBT and/or vBvP based on a log Dow < 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. Pharmacokinetic properties: Metabolism and Elimination. Summary of Product Characteristics Epivir (Lamivudine) 150mg film coated Tablets. ViiV Healthcare, May 2013.
3. Munro S. GR109714X: Determination of Physico-Chemical Properties. Report No. 93/GLX088/0358. Pharmaco-LSR, March 1994.
4. Cowlyn TC. GR109714X: Determination of Hydrolysis as a Function of pH. Report No. 93/GLX092/0266. Pharmaco-LSR, January 1994.
5. Jenkins CA. GR109714X: Acute Toxicity to Daphnia magna. Report No. 93/GLX090/0145. Pharmaco-LSR, February 1994.
6. Jenkins WR. GR109714X: Assessment of its Ready Biodegradability Modified Sturm Test. Report No. 93/GLX091/0141. Pharmaco-LSR, February 1994.
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8. Jenkins CA. GR109714X: Acute Toxcity to Rainbow Trout. Report No. 95/GLX173/0172. Pharmaco-LSR, March 1995.
9. Schaefer EC. Lamivudine: An Evaluation of Inherent Biodegradability Using the Zahn-Wellens/EMPA Test. Report No. 374E-123 Wildlife International Limited, July 2004.

10. Goodband TJ. Lamivudine: Daphnid, Ceriodaphnia dubia Survival and Reproduction Test. Report No. 1127/1214. Safepharm Laboratories Limited, November 2006.
11. Best N. Lamivudine: Toxicity to Activated Sludge in a Respiration Inhibition Test. Report No. 41500234. Harlan Laboratories Limited, June 2015.
12. Harris S. Lamivudine: Daphnia magna Reproduction Test. Report No. 41500232. Harlan Laboratories Limited, August 2015.
13. Ablit S. Lamivudine: Fish, Early Life Stage Toxicity. Report No. 41500231. Harlan Laboratories Limited, October 2015.
14. Sacker D. Lamivudine: Sediment-Water Chironomid Toxicity Test Using Spiked Sediment. Report No. WV65TS. Envigo Research Limited, January 2017.
15. Grist A. Lamivudine: Aerobic Transformation in Aquatic Sediment Systems. Report No. TMR0048. Harlan Laboratories Limited, February 2017.

Zidovudin

Miljörisk: Risk för miljöpåverkan av zidovudin kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.
Nedbrytning: Zidovudin är potentiellt persistent.
Bioackumulering: Zidovudin 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) = $(A*10^{9}*(100-R)/(365*P*V*D*100) = 1.5*10^{-6}*A(100-R)$

PEC = 8.1 x 10^{-5} µg/L

Where:
A = 0.81 kg (total sold amount API in Sweden year 2020, data from IQVIA).
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

Green Algae:
No data

Water flea (Daphnia magna):
Acute toxicity
EC50 48 h (immobility) > 1,000,000 µg/L (OECD 202) (Reference 6)
NOEC > 1,000,000 µg/L

Water flea (Daphnia magna):
Chronic toxicity
EC50 21 days (reproduction) > 100,000 µg/L (OECD 211) (Reference 7)
NOEC = 16,000 µg/L

Rainbow Trout:
Acute toxicity
No data

Other ecotoxicity data:
EC50 3 hours (Inhibition) =102,000 µg/L (OECD 209) (Reference 5)

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

Environmental risk classification (PEC/PNEC ratio)

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

Degradation

Biotic degradation

Ready degradability:
0.23% degradation in 28 days (OECD 301B) (Reference 3)

Inherent degradability:
0% degradation in 28 days (OECD 302B) (Reference 4)
50% primary (loss of parent) degradation in 3 days

Abiotic degradation

Hydrolysis:
Half-life, pH 7 > 1 year (OECD 111) (Reference 7)

Photolysis:

No data

Justification of chosen degradation phrase:
Zidovudine is not readily biodegradable nor inherently biodegradable. The phrase “Zidovudine is potentially persistent” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Log Kow = 0.06 (TAD 3.02) (Reference 7)

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

Excretion (metabolism)

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucoronidated metabolite. The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing. Renal clearance of zidovudine greatly exceeds creatinine clearance, indicating that significant tubular secretion takes place. (Reference 2)

PBT/vPvB assessment

Zidovudine 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). Zidovudine does not fulfil the criteria for PBT and/or vBvP based on a log Kow < 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. Pharmacokinetic properties: Metabolism and Elimination. Summary of Product Characteristics Retrovir (Zidovudine) 100mg Capsules. ViiV Healthcare, May 2013.
3. Gorman M. Aerobic Biodegradaion in Water using C14 Zidovudine. Report No. 41035. ABC Laboratories Limited, April 1994.
4. Ziegenfuss S. Zidovudine (GR63367X): Aerobic Biodegradation in Activated Sludge. Report No. ERL-2001-024. GlaxoSmithKline Environmental Laboratory, February 2002.
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7. Material Safety Data Sheet for Retrovir (Zidovudine) Tablets. SDS number 127089. ViiV Healthcare plc, April 2011.