

## Combivir®

M R F<sub>f</sub>

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:

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

$$PEC = 0.028 \mu\text{g/L}$$

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 =  $10 \cdot 10^6$

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 capricornutum):*

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 (Juvenile Oncorhynchus 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 ( $\mu\text{g/L}$ ) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fish (= 10,000  $\mu\text{g/L}$ ) has been used for this calculation since it represents the lowest value for all three tested species.*

#### **Environmental risk classification (PEC/PNEC ratio)**

$\text{PEC/PNEC} = 0.028/1,000 = 2.80 \times 10^{-5}$ , i.e.  $\text{PEC/PNEC} \leq 1$  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% degradation in soil (TAD 3.12) (Reference 3)

##### **Simulation studies:**

*Water-sediment study:*

50% ( $\text{DT}_{50}$ ) decline (total system) = 22-29 days (OECD 308) (Reference 14)

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

$\text{CO}_2$  = 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  $\text{DT}_{50}$  < 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.
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7. Jenkins CA. GR109714X: Determination of 72-hour EC50 to Green Alga. Report No. 95/GLX174/0358. Pharmaco-LSR, March 1995.
8. Jenkins CA. GR109714X: Acute Toxicity 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. Safeparm 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:

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

$$\text{PEC} = 8.1 \times 10^{-5} \mu\text{g/L}$$

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 =  $9 \cdot 10^6$

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 glucuronidated 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 Biodegradation 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.
5. Koper CM. Acute Toxicity of GR63367X (Zidovudine) to Activated Sludge Microorganisms. PEET-2001-066. GlaxoSmithKline Environmental Laboratory, February 2002.
6. Ziegenfuss MC. Toxicity of GR63367X (Zidovudine) to Daphnia magna. PEET-2002-001. GlaxoSmithKline Environmental Laboratory, January 2002.
7. Material Safety Data Sheet for Retrovir (Zidovudine) Tablets. SDS number 127089. ViiV Healthcare plc, April 2011.