

Kivexa

GlaxoSmithKline

Filmdragerad tablett 600 mg/300 mg

(orange, kapselformad, märkt GS FC2 på ena sidan)

Antiviralt medel

Aktiva substanser:

Abakavir

Lamivudin

ATC-kod:

J05AR02

Läkemedel från GlaxoSmithKline omfattas av
Läkemedelsförsäkringen.

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

Miljöpåverkan

Abakavir

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

Nedbrytning: Abakavir är potentiellt persistent.

Bioackumulering: Abakavir har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.096 \mu\text{g/L}$$

Where:

A = 642.87 kg (total sold amount API in Sweden year 2016, data from Quintiles IMS). Total volume of Abacavir sulphate = 734.98 = 627.34 Kg of abacavir free base. Total volume of Abacavir hydrochloride monohydrate = 17.51 = 15.53 Kg of abacavir free base. Total abacavir = 627.34 + 15.53 = 642.87 Kg.

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 (Selenastrum caprocornutum):

IC50 72h (growth) = 57,400 $\mu\text{g/L}$ (OECD 201) (Reference 8)

NOEC = 30,000 $\mu\text{g/L}$

Water flea (Daphnia magna):

Acute toxicity

EC50 48 h (immobility) = 139,000 µg/L (OECD 202) (Reference 3)

NOEC = 79,000 µg/L

Water flea (Ceriodaphnia dubia):

Chronic toxicity

EC50 7 days (reproduction) = 10,000 µg/L (EPA 1002) (Reference 11)

NOEC = 5,600 µg/L

Fathead Minnow (Juvenile Pimephales promelas):

Acute toxicity

LC50 96 h (lethality) > 95,000 µg/L (OECD 203) (Reference 9)

NOEC = 95,000 µg/L

Chronic Toxicity

NOEC 32 days (mortality) = 10,000 µg/L (OECD 210) (Reference 12)

Other ecotoxicity data:

Microorganisms in activated sludge

EC50 3 hours (Inhibition) > 71,400 µg/L (OECD 209) (Reference 7)

Chironomid (Chironomus riparius)

NOEC 28 days (reproduction) = 100,000 µg/kg (OECD 218)
(Reference 14)

PNEC = 5,600/10 = 560 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for water flea (= 5,600

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)

$PEC/PNEC = 0.096/560 = 1.71 \times 10^{-4}$, i.e. $PEC/PNEC \leq 1$ which justifies the phrase "Use of abacavir has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:

27% degradation in 28 days (OECD 301B) (Reference 5)

Inherent degradability:

100% primary (loss of parent) degradation in 14 days (OECD 302B) (Reference 10)

Data on the evaluation of degradation products is not available and therefore loss of parent API does not inform summary degradation phrase.

Simulation studies:

Water-sediment study:

50% (DT_{50} parent) degradation in 9.10 - 15.0 days (OECD 308)

(Reference 13)

Data on the evaluation of degradation products is not available and therefore loss of parent API in the OECD 308 is not used to assign a classification.

Non-extractable residue = 37.80% - 62.60%

Abiotic degradation

Hydrolysis:

Half-life, pH 7 > 1 year (TAD 3.09) (Reference 4)

Photolysis:

No Data

Justification of chosen degradation phrase:

Abacavir is not readily biodegradable nor inherently biodegradable. The phrase "Abacavir is potentially persistent" is thus chosen.

Bioaccumulation

Partitioning coefficient:

Log Dow = 1.20 at pH 7 (OECD 107) (Reference 3)

Log Dow at pH 5 = 0.90

Log Dow at pH 7 = 1.20

Log Dow at pH 9 = 1.20

Justification of chosen bioaccumulation phrase:

Since $\log P_{ow} < 4$, the substance has low potential for bioaccumulation.

Excretion (metabolism)

Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the

5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. The metabolites are excreted in the urine.

The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces (Reference 2).

PBT/vPvB assessment

Abacavir 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). Abacavir 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 Ziagen (Abacavir) 300mg Film Coated Tablets. ViiV Healthcare UK Ltd., March 2013.

3. Sydney P. 1592U89: Determination of the Physico-Chemical Properties. Report No. 96/GLX179/1022. Huntingdon Life Sciences Ltd, October 1997.
4. Sydney P. 1592U89: Determination of Hydrolysis as a Function of pH. Report No. 96/GLX181/0864. Huntingdon Life Sciences Ltd, October 1997.
5. Jenkins WR. 1592U89: Activated Sludge – Respiration Inhibition Test. Report No. GLX180/970062. Huntingdon Life Sciences Ltd, September 1997.
6. Jenkins CA. 1592U89: Acute Toxicity to *Daphnia magna*. Report No. 96/GLX180/1068. Huntingdon Life Sciences Ltd, September 1997.
7. Jenkins WR. 1592U89: Biotic Degradation with a Composite Inoculum. Modified Sturm Test. Report No. GLX183/970063. Huntingdon Life Sciences Ltd, September 1997.
8. Swarbrick RH. Abacavir sulphate: Toxicity to Green alga *Selenastrum capricornutum*. Report No. BL7702/B. Brixham Environmental Laboratory, October 2004.
9. Swarbrick RH. Abacavir sulphate: Acute Toxicity to Rainbow trout *Oncorhynchus mykiss*. Report No. BL7703/B. Brixham Environmental Laboratory, October 2004.
10. Swarbrick RH and Smyth DV. Abacavir sulphate: Determination of Inherent Biodegradability (Zahn-Wellens Test). Report No. BL7704/B. Brixham Environmental Laboratory, March 2006.
11. Young BE and Kent SJ. Abacavir sulphate: Determination of the 3-brood (7 day) Chronic Toxicity of *Ceriodaphnia dubia*. Report No. BL8144/B. Brixham Environmental.
12. Ablitt, S. Abacavir hemisulphate: Fish, Early Life Stage Toxicity. Report No. 41500228. Envigo Research Limited, October 2015.

13. Unsworth, R and Carter, J. Abacavir hemisulphate: Aerobic Transformation in Aquatic Sediment Systems. Report No. TMR0047. Envigo Research Limited, November 2016.
14. Ablitt, S. Abacavir hemisulphate: Sediment-Water Chironomid Toxicity Test Using Spiked Sediment. Report No. VG43JK. Envigo Research Limited, February 2017.

Lamivudin

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

Nedbrytning: Lamivudin är potentiellt persistent.

Bioackumulering: Lamivudin har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.047 \mu\text{g/L}$$

Where:

A = 315.27 kg (total sold amount API in Sweden year 2015, 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)

$P = \text{number of inhabitants in Sweden} = 9 \cdot 10^6$

$V \text{ (L/day)} = \text{volume of wastewater per capita and day} = 200$ (ECHA default) (Reference 1)

$D = \text{factor for dilution of waste water by surface water flow} = 10$ (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 µg/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 = 0.047/1,000 = 4.70 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% degradation in soil (TAD 3.12) (Reference 3)

Simulation studies:

Water-sediment study:

50% (DT₅₀) decline (total system) = 22-29 days (OECD 308)

(Reference 14)

CO₂ = 8.50% - 12.60%

Non-extractable residue = 8.00% - 9.10%

Abiotic degradation

Hydrolysis:

Half-life, pH 7 > 1 year (OECD 111) (Reference 3)

Photolysis:

No data

Justification of chosen degradation phrase:

Lamivudine is not readily biodegradable nor inherently biodegradable. The phrase "Lamivudine is potentially persistent" 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.
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.