FASS

Kivexa

GlaxoSmithKline

Filmdragerad tablett 600 mg/300 mg
(orange, kapselformad, 20,1 x 9,1 mm, 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:

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

PEC = 0.096 µg/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 = $9 *10^{6}$

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 µg/L (OECD 201) (Reference 8)

NOEC = 30,000 µg/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 (Juvenilee 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 x 10^{-4}, i.e. PEC/PNEC ≤ 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 Pow < 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

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13. Unsworth, R and Carter, J. Abacavir hemisulphate: Aerobic Transformation in Aquatic Sediment Systems. Report No. TMR0047. Envigo Research Limited, November 2016.
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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:

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

PEC = 0.047 µg/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 = 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 (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 = 0.047/1,000 = 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% 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)

CO_2 = 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

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2. Pharmacokinetic properties: Metabolism and Elimination. Summary of Product Characteristics Epivir (Lamivudine) 150mg film coated Tablets. ViiV Healthcare, May 2013.
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