FASS

Juluca

MRx EF

GlaxoSmithKline

Filmdragerad tablett 50 mg/25 mg
(Rosa, ovala, bikonvexa tabletter, cirka 14 x 7 mm, präglade med ”SV J3T” på ena sidan.)

Virushämmande medel för systemiskt bruk, virushämmande medel mot hiv-infektioner, kombinationer.

Aktiva substanser (i bokstavsordning):
Dolutegravir
Rilpivirin

ATC-kod:
J05AR21

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

Miljöpåverkan

Dolutegravir

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

Nedbrytning: Dolutegravir är potentiellt persistent.
Bioackumulering: Dolutegravir 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) = $(A*10^{9}*(100-R)/(365*P*V*D*100) = 1.37*10^{-6}$ *A(100-R)

PEC = 1.08×10^{-2} µg/L

Where:

A = 78.90 kg (total sold amount API free base in Sweden year 2022, data from IQVIA). Total volume of Dolutegravir sodium 83.05 = 78.90 Dolutegravir free base. Total Dolutegravir = 78.90.

R = 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolys is 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 (Pseudokirchneriella subcapitata):

IC50 96h (biomass) = 233 µg/L (OECD 201) (Reference 5)
NOEC = 95 µg/L

Water flea (Daphnia magna):

Acute toxicity
EC50 48 h (immobility) > 6,430 µg/L (OECD 202) (Reference 6)

Water flea (Daphnia magna):

Chronic toxicity
NOEC 21 days (reproduction) = 834 µg/L (OECD 211) (Reference 7)

Rainbow Trout:

Acute toxicity
No data

Fathead minnow (Juvenile Pimephales promelas):

Chronic toxicity
NOEC 28 days (mortality) = 220 µg/L (OECD 210) (Reference 8)

Other ecotoxicity data:

Chironomid (Chironomus riparius)
NOEC 28 days (reproduction) = 858,000 µg/kg (OECD 218) (Reference 9)

Microorganisms in activated sludge
EC50 3 hours (Inhibition) = 24,000 µg/L (OECD 209) (Reference 3)

Terrestrial toxicity

Earthworm (Eisenia foetida)

LC50 14 days (mortality) > 1,000,000 µg/kg (OECD 207) (Reference 12)
NOEC = 1,000,000 µg/kg

Collembola (Folsomia candida)

NOEC 28 days (reproduction) = 29,000 µg/kg (ISO 11267:1999) (Reference 13)

Soil microorganisms

NOEC = 984,000 µg/kg (OECD 216) (Reference 14)

Onion (Allium cepa), Pea (Pisum sativum)

NOEC 23 days (emergence) = 12,000 µg/kg (OECD208) (Reference 15)

PNEC = 95/10 = 9.50 µg/L
PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for green alga (= 95 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 = $1.08 \times 10^{-2}/9.5 = 1.14 \times 10^{-3}$, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of dolutegravir has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:
No data

Inherent degradability:
0% degradation in 28 days (OECD 302B) (Reference 10)
18% primary degradation of parent in 28 days
This substance is not inherently biodegradable.

Simulation studies:

Water-sediment study:
50% (DT50) degradation in > 1,000 days (OECD 308) (Reference 11)
Non-extractable residue = 8.70% - 9.30%

Soil Degradation:
Aerobic transformation in soil (OECD 307) (Reference 16)

Degradation rates
DT_{50} = 1,000 days
DT_{90} = 1,000 days
Non-extractable residue < 10%

Abiotic degradation

Hydrolysis:
No data

Photolysis:
No data

Justification of chosen degradation phrase:
Dolutegravir is not readily biodegradable nor inherently biodegradable. This substance is predicted to degrade in water sediment systems ≥ 120 days. Non-extractable residues represent < 10% of the total material. The phrase “Dolutegravir is potentially persistent” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Log Dow < 1 at pH 7 (OECD 107) (Reference 4)
Log Dow at pH 5 = -2.28
Log Dow at pH 7 = -2.45
Log Dow at pH 9 = -3.21

Justification of chosen bioaccumulation phrase:

Since log Dow < 4, the substance has low potential for bioaccumulation.

Excretion (metabolism)

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine,

represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose) (Reference 2).

Please, also see Safety data sheets on

http://www.msds-gsk.com/ExtMSDSlist.asp

References

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15. Muddiman KJ. GSK1349572A: Seedling Emergence and GrowthTest. Report No. 8252366. Smithers Viscient Limited, November 2012.
16. Dixon K and Fletcher T. [14C]-GSK1349572A: Aerobic Soil Metabolism and Degradation. Report No. 8252364. Smithers Viscient Limited, September 2012.

Rilpivirin

Miljörisk: Användning av rilpivirin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Rilpivirin är potentiellt persistent.
Bioackumulering: Rilpivirin 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 = 8.25 x 10^{-4} µg/L

Where:

A = 6.02 kg (total sold amount API in Sweden year 2022, data from IQVIA). Total volume of Rilpivirine sodium 6.49 = 5.90 sodium free base. Total Rilpivirine = 5.90 + 0.12 = 6.02.

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 (Pseudokirchneriella subcapitata):

NOEC 96h (growth ≥ 22 µg/L (OECD 201) (Reference 3)

Water flea (Daphnia magna):

Acute toxicity

No data

Water flea (Daphnia magna):

Chronic toxicity

NOEC 21 days (reproduction) = 32 µg/L (OECD 211) (Reference 4).

Rainbow Trout:

Acute toxicity

No data

Zebra Fish (Brachydanio rerio)

Chronic toxicity

NOEC 28 days (survival) = 20 µg/L (OECD 210) (Reference 5)

Other ecotoxicity data:

Chironomid (Chironomus riparius)

NOEC 28 days (reproduction) = 100,000 µg/kg (OECD 218) (Reference 6)

Microorganisms in activated sludge
EC50 3 hours (Inhibition) > 1,000,000 µg/L (OECD 209) (Reference 7)

Terrestrial toxicity

Earthworm (Eisenia foetida)
LC50 14 days (mortality) > 1,000,000 µg/kg (OECD 207) (Reference 8)
NOEC = 1,000,000 µg/kg

Collembola (Folsomia candida)
NOEC 28 days (reproduction) ≥ 1,000,000 µg/kg (ISO 11267:1999) (Reference 9)

Soil microorganisms
NOEC 28 days (nitrification) > 100,000 µg/kg (OECD 216) (Reference 10)

Plants
NOEC 15-17 days (emergence) = 1,000,000 µg/kg (OECD208) (Reference 11)

PNEC = 20/10 = 2 µg/L
PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for zebra fish (= 20 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 = 8.25 x 10^{-4}/2 = 4.13 x 10^{-4}, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of rilpivirine has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:
No data

Inherent degradability:
No data

Simulation studies:

Water-sediment study:
Total System: 50% (DT_{50}) dissipation in > 307 - 321 days (OECD 308) (Reference 12)
Non-extractable residue = 12.70% - 14.40%

(Organic matter fractionation of the bound residues showed that the majority of the radioactivity was associated with the insoluble fraction (humin)).

Extraction with acetonitrile/water (4/1; v/v), up to three times (from the start to day 28); acetone/water (4/1; v/v), up to three times (days 58 to 120). Reflux extraction with 0.1 M HCl / acetonitrile (1:1; v/v) at day 120.

Soil Degradation:
Aerobic transformation in soil (OECD 307) (Reference 13)

Degradation rates

DT_{50} = 71 - 232 days

DT_{90} > 365 days

Non-extractable residue = 12.5% – 15.1%

(Organic matter fractionation of the bound residues showed that the majority of the radioactivity was associated with the insoluble fraction (humin).

Abiotic degradation

Hydrolysis:
No data

Photolysis:
No data

Justification of chosen degradation phrase:
Rilpivirine is not readily biodegradable nor inherently biodegradable. This substance is predicted to degrade in water sediment systems ≥ 120 days. Non-extractable residues represent 12%-14% of the total material. The phrase “Rilpivirine is potentially persistent” is thus chosen.

Bioaccumulation

Partitioning coefficient:
Log D_{ow} = 4.66 (OECD 107) (Reference 14)

Bioconcentration:

BCF = 125.60 – 137.20 (OECD 305) (Reference 15)

Justification of chosen bioaccumulation phrase:
Since BCF is < 500, the substance has low potential for bioaccumulation.

Excretion (metabolism)

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system. The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of 14C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine. (Reference 2).

Please, also see Safety data sheets on

http://www.msds-gsk.com/ExtMSDSlist.asp

References

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