FASS

Padviram

M

Sandoz AS

Filmdragerad tablett 600 mg/200 mg/245 mg

Avregistreringsdatum: 2024-11-27 (Tillhandahålls ej) (Rosa, kapselformade tabletter omärkta på båda sidor med dimension cirka 11 mm x 22 mm.)

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

Aktiva substanser (i bokstavsordning):

Efavirenz
Emtricitabin
Tenofovirdisoproxil

ATC-kod:

J05AR06

För information om det avregistrerade läkemedlet omfattas av Läkemedelsförsäkringen, kontakta Läkemedelsförsäkringen.

Läs mer om avregistrerade läkemedel

Miljöpåverkan

Miljöinformationen för efavirenz är framtagen av företaget MSD för Stocrin®, Sustiva

Miljörisk: Användning av efavirenz har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Efavirenz är potentiellt persistent.
Bioackumulering: Efavirenz har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

PEC = 0.023 µg/L

Where:
A = 168 kg (total sold amount API in Sweden year 2022, data from IQVIA (Ref I.)
R = 0 % removal rate (worst case assumption)
P = number of inhabitants in Sweden = $10 * 10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. II)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. II)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green Algae (Selenastrum capricornutum) (FDA 4.01) (Ref. III)*:*
EC_{50} 12 day (growth rate) > 0.026 mg/L
NOEC 12 day (growth rate) = 0.026 mg/L
No effects seen up to highest concentration tested

Crustacean, water flea (Daphnia magna) (FDA 4.08) (Ref. IV)
Acute toxicity
EC_{50} 48 h (mortality) =1.1 mg/L

Chronic toxicity (OECD 211) (Ref. V)
NOEC 21 day (survival) = 0.16 mg/L

Fish, fathead minnow (Pimephales promelas) (OECD 210) (Ref. VI)

Chronic toxicity
NOEC 33 day (growth) = 0.07 mg/L

Fish, bluegill sunfish (Lepomis macrochirus) (FDA 4.11) (Ref. VII)
Acute toxicity
LC_{50} 96 h (mortality) = 0.85 mg/L

PNEC = 2.6 µg/L (0.026 mg/L / 10) based on the chronic NOEC for the algae and an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.023/2.6 = 0.0088, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of efavirenz has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Biodegradation Simulation Screening (FDA 3.11) (Ref. VIII)
Test results showed 12% biodegradation to CO_2 by Day 28

Abiotic degradation

Photolysis (EPA 795.70) (Ref. IX)
Test results indicate 85% photo-degradation over 16 days

Justification of chosen degradation phrase:
Efavirenz is degradable in biological systems and via photolysis, however the criteria for classification as degradable was not met. The phrase “Efavirenz is potentially persistent” is thus chosen.

Bioaccumulation

Bioconcentration Factor (OECD 305). (Ref. X)
Measured BCF values were 439 for low concentration (0.9 µg/L) and 454 for high concentration (9 µg/L)

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

References

I. Data from IQVIA ”Consumption assessment in kg for input to environmental classification - updated 2023 (data 2022)”.

II. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

III. Springborn Laboratories, Inc. 1997. "DMP 266 - Toxicity to the Freshwater Green Alga," Report No. 97-4-6954, Wareham, MA, 02 October 1997.

IV. Springborn Laboratories, Inc. 1997. "DMP 266 - Acute Toxicity to Daphnids (Daphnia magna) Under Static Conditions," Report No. 97-3-6906, Wareham, MA, 02 October 1997.

V. Springborn Smithers Laboratories, Inc. 2007. "Efavirenz (DMP 266) - Full Life-Cycle Toxicity Test with Water Flea, Daphnia magna, Under Static-Renewal Conditions," Study No. 12534.6301, Wareham, MA, 09 March 2007.

VI. Springborn Smithers Laboratories, Inc. 2007. "Efavirenz (DMP 266) - Early Life-Stage Toxicity Test with Fathead minnow (Pimephales promelas), Following OECD Guideling #210," Study No. 12534.6302, Wareham, MA, 08 February 2007.

VII. Springborn Laboratories, Inc. 1997. "DMP 266 - Acute Toxicity to Bluegill Sunfish (Lepomis macrochirus) Under Static-Renewal Conditions," Report No. 97-3-6907, Wareham, MA, 02 October 1997.

VIII. Springborn Laboratories, Inc. 1997. "DMP 266 - Determination of Aerobic Biodegradation in Water," Report No. 97-4-6937, Wareham, MA, 15 September 1997.

IX. Springborn Laboratories, Inc. 1997. "DMP 266 - Indirect Photolysis Screening Test with Synthetic Humic Water Following EPA/TSCA, 40 CFR Ch. 1, 795.70," Report No. 97-6-7017, Wareham, MA, 25 August 1997.

X. Springborn Smithers Laboratories, Inc. 2008. "Efavirenz (DMP 266) - Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (Lepomis macrochirus), Following OECD Guideline 305," Study No. 12534.6306, Wareha

Miljöinformationen för emtricitabin är framtagen av företaget Janssen-Cilag för Symtuza

Miljörisk: Användning av emtricitabin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Emtricitabin bryts ned långsamt i miljön.
Bioackumulering: Emtricitabin 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:

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

PEC = 0.068337792 µg/L

Where:

A = total actual API sales in Sweden for the most recent year 498.816 kg (total sold amount API in the most recent sales data for Sweden (2022) was distributed by IQVIA in 2023)

R = 0

P = number of inhabitants in Sweden = $10*10^{6}$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Reference VIII)

D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Reference VIII)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies
Algae (*Pseudokirchneriella subcapitata*) (guideline e.g. OECD 201) [Reference I]:
$E\gamma C_{50}$ 72 h (yield) > 110 mg/L
NOECγ (yield) ≥ 110 mg/L
E_rC_{50} 72 h (growth) > 110 mg/L
$NOEC_r$ (growth) ≥ 110 mg/L

Crustacean (Daphnia magna) (water-flea) (guideline e.g. OECD 211) [Reference II]:
Acute toxicity
Not available
Chronic toxicity

NOEC 21 days ≥ 110 mg/L (Reproduction)

Fish:
Acute toxicity
No data available

Chronic toxicity

Fish early life stage test with fathead minnow (*Pimephales promelas*) (guideline e.g. OECD 210) [Reference III]:

NOEC 28 days = 6.10 mg/L (growth, weight)

Other ecotoxicity data:
Activated sludge respiration inhibition test (guideline e.g OECD 209) [Reference IV]

EC_{50} 3h > 1000 mg/L
NOEC 3h ≥ 1000 mg/L

PNEC (µg/l) = lowest NOEC/10, where 10 is the assessment factor used. NOEC for fathead minnow *Pimephales promelas* of 6.10 mg/L has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 6.10mg/L/10 = 610 µg/L

Environmental risk classification (PEC/PNEC ratio)
PEC/PNEC = 0.068337792/610 = 0.000112029 i.e. PEC/PNEC ≤ 0,1

The calculated PEC/PNEC ratio is < 0.1.
Use of emtricitabine has been considered to result in insignificant environmental risk.

Degradation
Biotic degradation
Ready degradability:
Emtricitabine was investigated for its ready biodegradation in a 28-day Closed Bottle test according to OECD 301D [Reference V]:
Result: Not readily biodegradable.

Inherent degradability: -
Simulation studies:
Aerobic degradation in aquatic sediment systems

Emtricitabine was investigated for its aerobic degradation in a 100-day aquatic sediment test, according to OECD 308 [Reference VI].

Distribution
Emtricitabine was degraded at a moderate rate under the aerobic water sediment conditions of this study. Emtricitabine decreased from an average of 102.9 and 106.7% of applied radioactivity on day 0 to 66.0 and 14.5% of applied radioactivity at study termination (day 100) for the aerobic Taunton River and Weweantic River sediments, respectively. Percent of applied radioactivity (11.7 and 54.3%, respectively) was converted

to 14CO2 in the Taunton River aerobic and Weweantic River aerobic water/sediments (sandy loam and sand), respectively.
Fumigation/extraction biomass results for the aerobic sediments were typical and confirmed a viable microbial population was present over the course of the study.

The whole system DT_{50} was calculated using single first-order (SFO) kinetics. The primary FTC degradation product was CO_2.
Dissipation half life times total system:
Taunton River: DT_{50} = 150.65 days
Weweantic River: DT_{50} = 35.91 days

Transformation
Overall mass balance for the transformation of emtricitabine in the aerobic sediment/water systems: the average mass balance ranged from 95.4 to 108.3% of the applied radioactivity for the samples tested over the course of the 100-day study.
Mass Balance (% Applied radioactivity) - [14C]FTC Overall Average & Average Range:

	Mass Balance (% AR)	
[^{14}C]FTC	Overall Average	Average Range
Taunton River (TR) Aerobic	101.3	95.4 – 106.0
Weweantic River (WR) Aerobic	102.7	95.7 – 107.4

Evolution of 14CO2 reached 11.7% of the applied radioactivity for the Taunton River aerobic test samples and 54.3% of the applied radioactivity for the Weweantic River aerobic test samples by day 100. Negligible quantities of [14C] were detected in the volatile organic compound traps.

Conclusion for degradation:
Emtricitabine is slowly degraded in the total system of the Weweantic River (DT50 = 35.91 days),but is potentially persistent in the total system of the Taunton River (DT50 = 150.65 days). Due to two different degradation phrases the conclusion is that Emtricitabine is slowly degraded in the environment.

Abiotic degradation
Hydrolysis: -
Photolysis: -

Bioaccumulation
Partition coefficient octanol/water:
The partition coefficient octanol/water of emtricitabine was determined according to OECD 107 [Reference VII]

Log P_{ow} = -0.693, -0.670, -0.693 at pH 4, 7 and 10 respectively.

Log P_{ow} = -0.670 at pH 7, so this Log P_{ow} is < 4 at pH 7 which result in following conclusion: Emtricitabine has low potential for bioaccumulation.

Bioconcentration factor (BCF):

No data available

Conclusion for bioaccumulation: Emtricitabine has low potential for bioaccumulation.

Excretion (metabolism)

-

PBT/vPvB assessment

	PBT-criteria	Results for Emtricitabine
Persistence	Half-life in freshwater: DT_{50} > 40 days Half-life in sediment: DT_{50} > 120 days	$DT_{50,system}$ = 35.91- 150.65 days
Bioaccumulation	BCF > 2000	Emtricitabine has low potential for bioaccumulation.
Toxicity	Chronic NOEC < 10 µg/L	$NOEC_{algae}$ ≥ 110 mg/L $NOEC_{daphnia}$ ≥ 110 mg/L $NOEC_{fish}$ = 6.10 mg/L

Conclusion for PBT-assessment:
According to the established EU-criteria, emtricitabine should not be regarded as a PBT substance.

References

I. Acute Toxicity of Emtricitabine to the Freshwater Green Alga *Pseudokirchneriella subcapitata* Following OECD Guideline 201; Study Report Number TX-162-2002.
II. Emtricitabine – Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static Renewal Conditions, Following OECD Guideline Number 211; Study Report Number TX-162-2006.
III. Early Life-Stage Toxicity Test of Emtricitabine with Fathead Minnow (Pimephales promelas), following OECD Guideline 210; Study Report Number TX-162-2005.
IV. Activated Sludge Respiration Inhibition Test to Emtricitabine Following OECD Guideline 209; Study Report Number AD-162-2003.
V. Emtricitabine: Ready biodegradability Evaluation (OECD 301D); Study 1784.
VI. Emtricitabine – Aerobic and anaerobic Transformation in Aquatic Sediments Systems Following OECD Guideline 308; Study Report Number AD-162-2004.
VII. Determining the Partitioning Coefficient (n-Octanol/Water) of Emtricitabine by the Flask-shaking Method Following OECD Guideline 107; Study Report Number AD-162-2002.
VIII. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

Miljöinformationen för tenofovirdisoproxil är framtagen av företaget MSD för Delstrigo

Miljörisk: Användning av tenofovirdisoproxil har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Tenofovirdisoproxil bryts ned i miljön.
Bioackumulering: Tenofovirdisoproxil 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 = 0.07 µg/L

Where:
A = 505 kg (total sold amount API in Sweden year 2021, data from IQVIA) (Ref. I)
R = 0 % removal rate (worst case assumption)
P = number of inhabitants in Sweden = $10*10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. II)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (Ref. II)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Green Algae (Pseudokirchneriella subcapitata) (OECD 201) (Reference III):
EC50 72h = 69 mg/L (growth rate)
NOEC 72h = 18 mg/L

Crustacean, water flea (Daphnia magna) (OECD 211) (Ref. IV):
Chronic toxicity
NOEC 21d = 12 mg/L (reproduction)

Fish, fathead minnow (Pimephales promelas) (OECD 210) (Ref. V):
Chronic toxicity
NOEC 32d = 9 mg/L
No effects noted for any endpoint (hatching, survival, growth)

PNEC = 900 µg/L (9 mg/L/ 10 based on the most sensitive NOEC for the fathead minnow and an assessment factor (AF) of 10)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.07/900 = 7.E-05, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of tenofovir disoproxil fumarate has been considered to result in insignificant environmental risk.

Biotic degradation

Biodegradation in Activated Sludge
3.66% to CO_2 in 28 days (OECD 314B) (Ref VI)

[^{14}C] Tenofovir DF was evaluated for biodegradability in wastewater according to OECD Guideline 314B. Activated sludge was dosed with approximately 1 mg/L [^{14}C] tenofovir DF. [^{14}C] Tenofovir DF underwent partial primary and ultimate biodegradation over the course of the 28-day study. Mass balance of the biotic sludge system ranged from 94.1 to 100% of the applied radioactivity (% AR). Ultimate biodegradation (conversion to CO_2) at 28 days was 3.66% AR in the biotic activated sludge test solution and did not occur in the abiotic activated sludge test solutions. [^{14}C] Tenofovir DF was detected in the biotic sludge at 102%

AR on day 0, decreased to 31.6% on day 14, and was not detected through Day 28. One region of radioactivity and a polar region >10% AR were observed in the HPLC analyses of the biotic sludge starting on Day 3. The elimination rate constant, k_e, was -0.1628 day^{-1}.

Sediment Transformation (OECD 308) (Ref. VII):
DT_{50} (total system) = 1.68 – 3.4 days

Aerobic biodegradation of [^{14}C] tenofovir DF was also evaluated in two sediment/water systems at 20°C for 28 days following OECD Guideline 308. Sediment/water systems were dosed with 1 mg/L [^{14}C] tenofovir DF. Carbon dioxide (CO_2) produced due to biodegradation was trapped and measured over the test period. Sediment and water samples were extracted and analyzed to determine extractable radioactivity. Water/sediment samples were analyzed at 0, 1, 3, 7, 14, and 28 days of incubation for the Taunton River and Weweantic River test systems. Sediment samples were extracted once with approximately 150 mL of 85/11/4 acetone/purified reagent water/phosphoric acid (v/v/v) and hand shaken to transfer the sediment fraction to a 250-mL Nalgene bottle. The sediment sample was placed on a shaker table at approximately 200 rpm for 10 minutes and then centrifuged at 3000 rpm for 10 minutes. The sediment extract was transferred to a graduated cylinder, the volume recorded, and analyzed by LSC. The extraction procedure was repeated up to two more times for each sampling interval for a total of up to three extractions. The extracts were then combined and analyzed by LSC. The extraction process was terminated after the first extraction for the day 0 sampling interval since >95% AR was recovered from test samples. Day 0 sediment extracts contained <2.5% AR for each sample and therefore, no further analysis was conducted.

The post-extraction solids (PES) were combusted and analyzed by LSC for determination of non-extractable residues. The volatile trapping solutions were analyzed by LSC for determination of $^{14}CO_2$ and volatile organics. Non-extractable residues in day 28 PES samples were additionally characterized by extraction with a polar and non-polar solvent.

Average recovery ranged from 88.4 to 101% over the course of the study for both the Taunton River and Weweantic River test systems.

The results showed that [^{14}C] tenofovir DF was degraded in total water/sediment systems with an observed half-life of 1.68 and 3.4 days at 20°C in the Taunton and Weweantic Systems, respectively. Corresponding half-lives at 12^{o}C were calculated using the Arrhenius equation and were determined to be 4.74 and 9.09 days (Total System). Half-lives for the water layer were 1.26 days and 3.38 days at 20°C in the Taunton and Weweantic Systems, respectively. Corresponding half-lives at 12°C were calculated using the Arrhenius equation and were determined to be 2.88 and 7.44 days (Water Layer). Half-lives for the sediment extracts were 0.789 days and 5.83 days at 20°C in the Taunton and Weweantic Systems, respectively. Corresponding half-lives at 12°C were calculated using the Arrhenius equation and were determined to be 1.68 and 12.4 days (Sediment Extracts). Tenofovir DF does not undergo significant mineralization and CO_2 production during the study ranged from 2.0 to 2.3%.

Evidence of primary biodegradation was observed for [^{14}C] tenofovir DF in the aerobic water/sediment test systems. Three major transformation products (≥10% AR) developed in both the Taunton River and Weweantic River total systems over the course of the study and were designated as polars, TP 2, and TP 4. An additional major transformation product (≥10% AR) developed in the Taunton River total system and

was designated as TP 1. These transformation products were identified by LC-MS/MS. Other minor peaks, not exceeding 5.0% AR at more than one interval, were observed in the water layer and sediment extracts and were not characterized further.

Justification of chosen biotic degradation phrase:
Since half-life < 32 days for total system, tenofovir disoproxil fumarate is degraded in the environment.

Bioaccumulation

Partitioning coefficient (OECD 107) (Ref.VIII):
Log Kow = 1.06 at pH 7

Justification of chosen bioaccumulation phrase:
Since log Kow < 4, tenofovir disoproxil fumarate has low potential for bioaccumulation.

References

I. Data from IQVIA ”Consumption assessment in kg for input to environmental classification - updated 2022 (data 2021)”.

II. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

III. Smithers Viscient, 2019. “Tenofovir DF - 72-hour toxicity test with the freshwater green alga, *Raphidocelis subcapitata*: OECD 201”. Wareham (MA): Smithers Viscient; 25 Mar 2019. 66 p. Smithers Viscient Study No. 359.7085.

IV. Smithers Viscient, 2019. “Tenofovir DF - full life-cycle toxicity test with water fleas, *Daphnia magna*, under flow-through conditions: OECD 211”. Wareham (MA): Smithers Viscient; 7 Feb 2019. 68 p. Smithers Viscient Study No. 359.7088.

V. Smithers Viscient, 2019. “Tenofovir DF - early life-stage toxicity test with fathead minnow (*Pimephales promelas*): OECD 210”. Wareham (MA): Smithers Viscient; 16 Apr 2019. 101 p.Smithers Viscient Study No. 359.7087.

VI. Smithers Viscient, 2019. “[14C]Tenofovir DF - determination of the biodegradability of a test substance in activated sludge based on OECD Method 314B”. Wareham (MA): Smithers Viscient; 19 Mar 2019. 64 p. Smithers Viscient Study No. 359.7082.

VII. Smithers Viscient, 2019. “[14C]Tenofovir DF - aerobic transformation in aquatic sediment systems: OECD 308”. Wareham (MA): Smithers Viscient; 15 Apr 2019. 198 p. Smithers Viscient Study No. 359.7083.

VIII. Smithers Viscient, 2019. “Tenofovir DF - determining the partitioning coefficient (n-octanol/water) by the shake-flask method following OECD guideline 107”. Wareham (MA): Smithers Viscient; 21 Jan 2019. 76 p. Smithers Viscient Study No. 359.7080.