

Tigecycline Mylan

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Mylan

Pulver till infusionsvätska, lösning 50 mg
(Orange till orange-röd, frystorkad kaka eller pulver, fri från
synliga tecken på kontaminering.)

Antibakteriella medel för systemiskt bruk, tetracykliner.

Aktiv substans:

Tigecyklin

ATC-kod:

J01AA12

Läkemedel från Mylan omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för tigecyklin är framtagen av företaget Pfizer för Tygacil®

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

Nedbrytning: Tigecyklin bryts ned i miljön.

Bioackumulering: Tigecyklin har hög potential att bioackumuleras.

Detaljerad miljöinformation

Physical properties

Solubility⁴: $>294 \times 10^6 \mu\text{g/L}$
pKa: Basic: 4.4, 8.9, 9.5; Acidic: 2.8, 7.4. Net charge is 0 at pH 8.
Vapor pressure: $1.21 \times 10^{-27} \text{ Pa}$
Molecular weight⁴: 585.65 Da

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$\cdot A(100 - R)$

$$\text{PEC} = 4.9 \times 10^{-6} \mu\text{g/L}$$

Where:

A =	0.06 kg (total sold amount API in Sweden year 2020, data from IQVIA) ³ .
R =	40 % removal rate as calculated with SimpleTreat 4.0 using a sludge sorption coefficient (Kd) of 6630 (Reference OECD 106) and a K _{biodeg} of 0 (Reference OECD 302B)
P =	

	number of inhabitants in Sweden = $10 \cdot 10^6$
V (L/day) =	wastewater volume per capita and day = 200 (ECHA default) ¹
D =	factor for wastewater dilution by surface water flow = 10 (ECHA default) ¹

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Activated sludge microorganisms (guideline OECD 209)*⁵

EC₅₀ (respiration inhibition) = 58 000 µg/L

Green alga (Pseudokirchneriella subcapitata) (guideline OECD 201)

6

EC₂₀ 72 h (growth rate, chronic toxicity) = 1170 µg/L

EC₅₀ 72 h (growth rate, chronic toxicity) = 1650 µg/L

*Daphnids (Daphnia magna) (guideline OECD 211)*⁷

NOEC 21 days (reproduction, chronic toxicity) = 2100 µg/L

EC₅₀ 21 days (reproduction, chronic toxicity) = 3600 µg/L

*Fathead Minnow (Pimephales promelas) (guideline OECD 210)*⁸

NOEC 32 days (survival, chronic toxicity) = 22 µg/L

LOEC 32 days (survival, chronic toxicity) = 54 µg/L

*Midge (Chironomus riparius) (guideline OECD 218)*⁹

NOEC 28 days (emergence, chronic toxicity) = 94 000 µg/kg

LOEC 28 days (emergence, chronic toxicity) = >94 000 µg/kg

Based on the lowest NOEC for the species *Pimephales promelas* and using the assessment factor² of 10, the PNEC is calculated to $22/10 = 2.2 \text{ µg/L}$.

Environmental risk classification (PEC/PNEC ratio)

$\text{PEC/PNEC} = 4.9 \times 10^{-6} / 2.2 = 2.2 \times 10^{-6}$, i.e. $\text{PEC/PNEC} \leq 0.1$ which justifies the phrase "Use of tigecycline has been considered to result in insignificant environmental risk."

Adsorption (guideline OECD 106)¹⁰

Solid	K_d (L/Kg)	K_{oc} (L/Kg)
Activated sludge (Wareham WWTP)	6630	15 100

Degradation

Biotic degradation

Inherent degradability (guideline OECD 302)¹¹

36% biodegradation after 46 days. It does not pass the FASS pass level of 70% degradation in 7 days, and is thus classified by FASS as not inherently biodegradable.

Water-sediment transformation simulation (guideline OECD 308)¹²

Length of study: 102 days

High organic sediment system: Taunton river

Low organic sediment system: Weweantic river

Sediment extraction solvent: Acetonitrile:hydrochloric acid (99:1, v/v) and acetonitrile:water:hydrochloric acid (80:20:1.0, v/v/v)
 Supplemental extraction solvents: None

The results from the study are shown in the table below.

Data on day 102 at 20 °C	Taunton river	Weweantic river
<i>Total system</i>		
Half-life (days)	1.1	0.9
Total ¹⁴ CO ₂ (% of AR)	39.9	36.7
% Parent (% of AR)	0.0	0.0
<i>Aerobic Water Layer</i>		
Half-life (days)	1.1	0.9
Parent (% of AR)	0.0	0.0
<i>Sediment Layer</i>		
Bound/NER (% of AR)	12.8	8.7
Extractables (% of AR)	21.3	23.4
Parent (% of AR)	0.0	0.0

ND = not detected, NER = non-extractable residues, AR = applied radioactivity

Justification of chosen degradation phrase

As the total system DT_{50} value (water-sediment transformation simulation, OECD 308) was calculated to 1.1 days or less, it corresponds to the degradation phrase "tigecycline is degraded in the environment".

Bioaccumulation

Partitioning coefficient (guideline OECD 117)¹⁴

Mean $\log P_{ow}$ is 6.7.

Justification of chosen bioaccumulation phrase

Since $\log P_{ow} > 4$, tigecycline has high potential for bioaccumulation.

References

1. ECHA, European Chemicals Agency. 2016 Guidance on information requirements and chemical safety assessment chapter R16.
2. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment chapter R10.
3. IQVIA KG Consumption 2020 report.
4. Tygacil Module 3.2.S.1 General properties. Jan 2016.
5. Study report 2727-WY: Tigecycline: Activated sludge respiration inhibition test. July 2004.
6. Study report MSL 05-0002: Tigecycline: A study on the toxicity to algae (*Pseudokirchneriella subcapitata*). September 2005.

7. Study report 13554.6191: Tigecycline – Full life-cycle toxicity test with water fleas, *Daphnia magna*, under flow-through conditions, following OECD 211. July 2009.
8. Study report 13554.6190: Tigecycline – Early life-stage toxicity test with fathead minnow, *Pimephales promelas*, following OECD guideline 210. July 2009.
9. Study report 13554.6198: Tigecycline – Toxicity test with sediment-dwelling midges (*Chironomus riparius*) under static conditions, following OECD guideline 218. July 2009.
10. Study report 13554.6192: [¹⁴C]Tigecycline – Determining the adsorption coefficient (K_{oc}) following OECD guideline 106. August 2009.
11. Study report 2728-WY: Tigecycline: Determination of the inherent biodegradability (biotic degradation) using the Zahn-Wellens/EMPA test. July 2004.
12. Study report 13554.6193: [¹⁴C]Tigecycline – Aerobic transformation in aquatic sediment systems following OECD guideline 308. June 2010.
13. Study report 2723-WY: Tigecycline: Hydrolysis as a function of pH (preliminary test). July 2004.
14. Study report 2722-WY: Tigecycline: Partition Coefficient (n-Octanol/Water) High Performance Liquid Chromatography (HPLC) Method. July 2004.