FASS

Sunitinib STADA

MRF

STADA Nordic

Kapsel, hård 50 mg

(Gelatinkapsel på cirka 19,3 mm ± 0,5 mm med karamellfärgat lock och underdel. Märkt med ”50 mg” på underdelen i vit tryckfärg. Kapseln innehåller gula till orange granulat.)

Övriga cytostatiska/cytotoxiska medel, proteinkinashämmare

Aktiv substans:

Sunitinib

ATC-kod:

L01EX01

Läkemedel från STADA Nordic omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för sunitinib är framtagen av företaget Pfizer för SUTENT, SUTENT®

Miljörisk: Användning av sunitinib har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Sunitinib bryts ned i miljön.
Bioackumulering: Sunitinib har låg potential att bioackumuleras.

Detaljerad miljöinformation

Biodegradation studies conducted in sludge indicate sunitinib will undergo limited degradation during the wastewater treatment process. Based on a sludge sorption coefficient (K_d) of 1340, 18% removal through sorption to sludge during the wastewater treatment process may be expected. Upon release of wastewater effluents into the aquatic environment, sunitinib residues will reside in the water and sediment compartments. Based on aqueous dissipation half-lives of 7.5 and 7.7 days, sunitinib is expected to rapidly dissipate from the water to the sediment with approximately 59% to 68% becoming irreversibly bound. Sediment half-life values for sunitinib were extrapolated beyond the 100-day test duration, and ranged from 118 - 169 days.

Physical properties[4,5]

Solubility at pH 1.2-6.8: 25×10^{-6} µg/L

Solubility at pH 7: 0.05×10^{-6} µg/L

Vapor pressure: $<1\times10^{-7}$ mmHg

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

PEC = 1.75×10^{-4} µg/L

Where:

A =	1.5565328 kg (total sold amount API in Sweden year 2021)[3]
R =	18% removal rate (due to loss by adsorption to sludge particles as calculated in the OECD 106 study [11]
P =	number of inhabitants in Sweden = 10×10^{6}
V (L/day) =	wastewater volume per capita and day = 200 (ECHA default)[1]
D =	factor for waste water dilution by surface water flow = 10 (ECHA default)[1]

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Activated sludge microorgansims (guideline OECD 209)[6]

EC_{15} (respiration inhibition) = 19 400 µg/L

EC_{50} (respiration inhibition) = 105 000 µg/L

Green alga (Raphidocelis subcapitata) (guideline OECD 201)[7]
EC_{50} 72 h (biomass, chronic toxicity) = 170 µg/L
NOEC 72 h (biomass, chronic toxicity) = 46 µg/L
EC_{50} 72 h (growth rate, chronic toxicity) = 320 µg/L
NOEC 72 h (growth rate, chronic toxicity) = 100 µg/L

Daphnids (Ceriodaphnia dubia) (guideline OECD 211)[8]
LOEC 7 days (reproduction, chronic toxicity) = 660 µg/L
NOEC 7 days (reproduction, chronic toxicity) = 320 µg/L

Fathead Minnow (Pimephales promelas) (guideline OECD 210)[9]
LOEC 32 days (growth, chronic toxicity) = 49 µg/L
NOEC 32 days (growth, chronic toxicity) = 27 µg/L

Midge (Chironomus riparius) (guideline OECD 218)[10]
LOEC 28 days (emergence, chronic toxicity) = 250 000 µg/kg
NOEC 28 days (emergence, chronic toxicity) = 125 000 µg/kg

Based on the lowest NOEC for the species *Pimephales promelas* and using the assessment factor[2] of 10, the PNEC is calculated to 27/10 = 2.7 µg/L.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 1.75×10^{-4} / 2.7 = 6.48×10^{-5}, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase ‘Use of sunitinib has been considered to result in insignificant environmental risk.’

Adsorption (guideline OECD 106)[11]

Solid		

	K_d (L/Kg)	K_{oc} (L/Kg)
Activated sludge (Wareham, MA, WWTP)	1340	5700
HOM soil (Ostlie East sandy clay loam)	6670	185 000
HOM soil (Don Uglem loam)	13 700	327 000
LOM soil (Mutchler sandy loam)	7820	412 000
LOM soil (Roger Myron loamy sand)	5290	481 000
LOM soil (Valley Montana clay)	7260	660 000

HOM = high organic matter, LOM = low organic matter

Using the formula $(0.165 \times K_d) / [(0.165 \times K_d) + 1000]$ where 0.165 represents the grams of sludge wasted per 1000 grams of wastewater treatment plants' aqueous effluent, we can calculate the ratio of the substance removed onto sludge solids during wastewater treatment. Based on the lowest sludge K_d value of 1340, the fraction of the substance estimated to be removed on wasted sludge is: $(0.165 \times 1340) / [0.165 \times 1340 + 1000] = 0.18 = 18\%$.

Degradation

Biotic degradation

Ready degradability (guideline OECD 301B)[12]

Tests of ready biodegradability are stringent tests that provide limited opportunity for acclimation and biodegradation to occur. The amount of CO_2 produced by the test substance (corrected for that evolved by the blank inoculum) during the 28 day long study is expressed as a percentage of the theoretical amount of CO_2 (TCO_2) that could have been produced if complete biodegradation of the test substance occurred. The test resulted in a 8.8% mineralisation for sunitinib in activated sludge and is therefore not considered to be readily biodegradable.

Simulation studies (guideline OECD 308)[13]

A 100 day long study was conducted to evaluate the degradability of the parent substance in two different sediment systems, Brandywine creek (high organic content) and Choptank River (low organic content) sediments. The sediments were extracted twice with acidified acetonitrile with 1% acetic acid (v/v) in the original transformation chambers using mechanical shaking.
The results from the study are shown in the table below.

Data on day 100	Brandywine creek	Choptank river
Total system		
Half-life (days)	11.8	11.4
Total $^{14}CO2$ (% of AR)	3.9	6.7
% Parent (% of AR)	8.9	11.3
Aerobic Water Layer		
Half-life (days)	7.5	7.7

Parent (% of AR)	ND	ND
Sediment Layer		
Half-life (days)	118	169
Bound/NER (% of AR)	67.7	59.2
Parent (% of AR)	8.9	11.3

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

WWTP degradation (guideline OECD 314B)[14]
The 28-day long study was conducted to evaluate the rate and extent of primary biodegradation and mineralization of the test substance in activated sludge fromthe Denton Wastewater Treatment Plant, Denton, Maryland, USA , i.e. an estimation on the removal of the substance from wastewater. The data from the study is shown below.

Parent compound at the end of the study: ND
Total mineralisation: 23.1 %
Adsorption to the activated sludge as non-extractable residues: 34.6 %
Total system DT_{50}: 69 hours

Abiotic degradation

Photolysis (guideline OECD 316)[15]

pH	**Environmental photolytic half-life (t1/2) in days**
5	1.58

7	1.15
9	0.52

Justification of chosen degradation phrase

As the total system DT_{50} value (water-sediment simulation study, OECD 308) was calculated to less than 12 days and considering the significant photodegradation (OECD 316) that can be expected in the environment, the degradation phrase ”Sunitinib is degraded in the environment.” is chosen.

Bioaccumulation

Partitioning coefficient (guideline OECD 107)[16]

pH	Log D_{ow}
5	1.28
7	1.03
9	3.51

Justification of chosen bioaccumulation phrase

Since log D_{ow} < 4 at pH 7, sunitinib has low 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 2021 report.
4. Sutent Module 3, Section 3.2.S.1.3 – General Properties. June 2005.
5. Hine, J. and Mookerjee PK. “The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions.” J. Org. Chem. 1975, 40:292-298.
6. Study report 2438.6558. Sutent – Determination of activated sludge respiration inhibition. January 2009.
7. Study report 2438.6463. Sutent – Acute toxicity to the freshwater green alga, *Pseudokirchneriella subcapitata*. November 2005.
8. Study report 2438.6466. Sutent – The life cycle toxicity test with daphnids, *Ceriodaphnia dubia*, under static-renewal conditions. November 2005.
9. Study report 2438.6556. Sutent – Early life-stage toxicity test with fathead minnow (*Pimephales promelas*), following OECD guideline #210. January 2009.
10. Study report 2438.6592. Sutent – Toxicity test with sediment-dwelling midges (*Chironomus riparius*) under static conditions, following OECD guideline 218. July 2011.
11. Study report 2438.6461. $^{[14C]}$SU-011248 – Determination of the adsorption coefficient (K_{oc}). August 2005.
12. Study report 260E-196. Sutent: Determination of ready biodegradability by the carbon dioxide evolution test method. March 2008.
13. Study report 260E-172. SU-011248: Aerobic transformation in aquatic sediment systems. February 2017.

14. Study report 260E-160. Sutent: Dieaway in activated sludge. December 2005.
15. Study report 2438.6473. $^{[14C]}$Sutent – Determination of photodegradation in water. February 2006.
16. Study report 260C-181. Determination of the *n*-octanol/water partition coefficient of sutent (sunitinib malate) by the shake flask method. February 2017.