

## Sunitinib Glenmark

M R F

Glenmark Pharmaceuticals Nordic

Kapsel, hård 50 mg

(Gelatinkapsel storlek 1 (längd ca 19,4 mm) med karamellfärgad över- och underdel, märkt "50 mg" i vit tryckfärg på underdelen och innehållande gula till orange granulat.)

Proteinkinashämmare

### Aktiv substans:

Sunitinib

### ATC-kod:

L01EX01

Läkemedel från Glenmark Pharmaceuticals 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<sup>4,5</sup>

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

Solubility at pH 7:  $0.05 \times 10^{-6}$  µg/L

Vapor pressure:  $<1 \times 10^{-7}$  mmHg

### Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 1.75 \times 10^{-4} \text{ } \mu\text{g/L}$$

Where:

A =	1.5565328 kg (total sold amount API in Sweden year 2021) <sup>3</sup>
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 = $10 \times 10^6$
V (L/day) =	wastewater volume per capita and day = 200 (ECHA default) <sup>1</sup>
D =	factor for waste water dilution by surface water flow = 10 (ECHA default) <sup>1</sup>

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

*Activated sludge microorganisms (guideline OECD 209)*<sup>6</sup>

EC<sub>15</sub> (respiration inhibition) = 19 400 µg/L

EC<sub>50</sub> (respiration inhibition) = 105 000 µg/L

*Green alga (Raphidocelis subcapitata) (guideline OECD 201)*<sup>7</sup>

EC<sub>50</sub> 72 h (biomass, chronic toxicity) = 170 µg/L

NOEC 72 h (biomass, chronic toxicity) = 46 µg/L

EC<sub>50</sub> 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)*<sup>8</sup>

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)*<sup>9</sup>

LOEC 32 days (growth, chronic toxicity) = 49 µg/L

NOEC 32 days (growth, chronic toxicity) = 27 µg/L

*Midge (Chironomus riparius) (guideline OECD 218)*<sup>10</sup>

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<sup>2</sup> of 10, the PNEC is calculated to  $27/10 = 2.7$  µg/L.

#### Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 1.75 \times 10^{-4} / 2.7 = 6.48 \times 10^{-5}$ , i.e.  $PEC/PNEC \leq 0.1$  which justifies the phrase 'Use of sunitinib has been considered to result in insignificant environmental risk.'

#### **Adsorption (guideline OECD 106)**<sup>11</sup>

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)*<sup>12</sup>

Tests of ready biodegradability are stringent tests that provide limited opportunity for acclimation and biodegradation to occur. The amount of CO<sub>2</sub> 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<sub>2</sub> (TCO<sub>2</sub>) 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)<sup>13</sup>*

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
<i>Total system</i>		
Half-life (days)	11.8	11.4
Total <sup>14</sup> CO <sub>2</sub> (% of AR)	3.9	6.7
% Parent (% of AR)	8.9	11.3
<i>Aerobic Water Layer</i>		
Half-life (days)	7.5	7.7
Parent (% of AR)	ND	ND
<i>Sediment Layer</i>		
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)<sup>14</sup>*

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 from the 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<sub>50</sub>: 69 hours

Abiotic degradation

*Photolysis (guideline OECD 316)<sup>15</sup>*

pH	Environmental photolytic half-life (t <sub>1/2</sub> ) in days
5	1.58
7	1.15
9	0.52

*Justification of chosen degradation phrase*

As the total system DT<sub>50</sub> 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)<sup>16</sup>

pH	Log D <sub>ow</sub>
5	1.28
7	1.03
9	3.51

### Justification of chosen bioaccumulation phrase

Since log D<sub>ow</sub> < 4 at pH 7, sunitinib has low potential for bioaccumulation.

## References

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16. Study report 260C-181. Determination of the *n*-octanol/water partition coefficient of sutent (sunitinib malate) by the shake flask method. February 2017.