

## Caprelsa

**M R F****Sanofi AB**

Filmdragerad tablett 100 mg

(rund, bikonvex, vit, filmdragerad, märkt "Z100" på ena sidan)

Proteinkinashämmare, övriga cytostatiska, cytotoxiska medel

**Aktiv substans:**

Vandetanib

**ATC-kod:**

L01EX04

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

## Miljöpåverkan

### Vandetanib

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

Nedbrytning: Vandetanib är potentiellt persistent.

Bioackumulering: Vandetanib har låg potential att bioackumuleras.

# Detaljerad miljöinformation

## Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

The PEC is based on following data:

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

$$\text{PEC } (\mu\text{g/L}) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

A (kg/year) = total sold amount API in Sweden year 2020, data from IQVIA.

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0

P = number of inhabitants in Sweden =  $1 \cdot 10^7$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default)(Ref 1)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default)(Ref 1)

(Note: The factor  $10^9$  converts the quantity used from kg to  $\mu\text{g}$ ).

$$A = 0.09 \text{ kg}$$

$$R = 0$$

$$\text{PEC} = 1.37 \cdot 10^{-6} \cdot 0.09 \cdot (100 - 0) = 0.0000123 \mu\text{g/L}$$

(Note: Whilst vandetanib is metabolised in humans, little is known about the ecotoxicity of the metabolites. Hence, as a worst case, for the purpose of this calculation, it is assumed that 100 % of excreted metabolites have the same ecotoxicity as parent vandetanib).

## Metabolism

After oral administration 69 % of vandetanib was excreted either as parent compound or metabolites. Approximately 44 % was excreted via faeces and 25 % via urine (Ref 2).

## Ecotoxicity Data

Endpoint	Species	Common Name	Method	Time	Result	Reference
EC50 - Based on Growth Rate	<i>Pseudo-kirchneriella subcapitata</i>	Green Algae	OECD 201	72 h	0.30 mg/L Note 1	3
NOEC - Based on Growth Rate					0.11 mg/L Note 1	
EC50 - Based on Immobilisation	<i>Daphnia magna</i>	Giant Water Flea	OECD 202	48 h	2.6 mg/L Note 4	4
NOEC - Based on Immobilisation					0.10 mg/L Note 4	

Endpoint	Species	Common Name	Method	Time	Result	Reference
EC50 - Based on Reproduction & Length	<i>Daphnia magna</i>	Giant Water Flea	OECD 211	21 d	>0.61 mg/L Note 1	5
NOEC - Based on Reproduction & Length					0.30 mg/L Note 1	
LOEC - Based on Reproduction & Length					0.61 mg/L Note 1	
NOEC - Based on Overall Endpoints Note 5	<i>Chironomus riparius</i>	Midge	OECD 218	28 d	100 mg/kg sediment (dry weight) Note 3	6
LOEC - Based on Overall Endpoints Note 5					100 mg/kg sediment (dry weight) Note 3	
LC50				96 h	4.1 mg/L	7

Endpoint	Species	Common Name	Method	Time	Result	Reference
	<i>Oncorhynchus mykiss</i>	Rainbow Trout	OECD 203		Note 4	
NOEC - Based on Mortality					2.5 mg/L Note 4	
NOEC - Based on Overall Endpoints	<i>Pimephales promelas</i>	Fathead Minnow	OECD 210	32 d	0.010 mg/L Note 4	8
LOEC - Based on Overall Endpoints					>0.010 mg/L Note 4	
EC50 - Based on Activated Sludge Respiration Inhibition	-	-	OECD 209	3 h	>100 mg/L Note 3	9
NOEC - Based on Activated Sludge Respiration Inhibition					10 mg/L Note 3	

## PNEC (Predicted No Effect Concentration)

Long term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on results from the assessment of the most sensitive species, fathead minnow (*Pimephales promelas*), NOEC = 10 µg/L and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 10).

$$\text{PNEC} = 10/10 \text{ µg/L} = 1.0 \text{ µg/L}$$

## Environmental risk classification (PEC/PNEC ratio)

$0.0000123 \text{ µg/L} / 1.0 \text{ µg/L} = 0.0000123$  i.e.  $\text{PEC/PNEC} < 0.1$  which justifies the phrase “Use of vandetanib has been considered to result in insignificant environmental risk”.

## Environmental Fate Data

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
Percentage Biodegradation	OECD 301F	10 mg/L Note 3	28 d	<5 %	11
Soil Dissipation Rate	OECD 307	Sandy Loam Soil	119 d	Bound rapidly to soil, no	

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
				degradation observed	12
		Clay Soil	119 d	Bound rapidly to soil, no degradation observed	
Percentage Mineralisation	OECD 308	HOM sediment (aerobic system)	98 d	<1 %	13
		LOM sediment (aerobic system)		<1 %	
		HOM sediment (anaerobic system)		<1 %	
		LOM sediment (anaerobic system)		<1 %	
			-	<11 days	

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
Dissipation Half lives from water*		HOM and LOM sediment (aerobic system)			
		HOM and LOM sediment (anaerobic system)	-	<11 days	
Sewage Adsorption Coefficient	OPPTS 835.1110	0.250 mg/L	-	Kd = 8400	14

HOM = High Organic Matter, LOM = Low Organic Matter

\*Only a small % of the Applied Radioactivity could be extracted from the sediment. Not possible to determine total system half-life.

## Biodegradation

Vandetanib is not readily biodegradable in accordance to the OECD 301F. There is evidence that the substance will strongly bind to sludge and sediment in the aquatic environment.

In the OECD 308 study, radiolabeled test substance was dosed into the overlying water and the subsequent dissipation from the water phase, and partitioning and/or degradation in the sediment, phase was observed over a 98 day test period. Aerobic and anaerobic test



systems containing water and sediment differing in organic carbon content were used in the study. Evidence from the study shows that vandetanib is likely to rapidly dissipate from the aqueous phase and partition into the solid phase in both aerobic and anaerobic systems. By Day 11, in both high organic matter (HOM) and low organic matter (LOM) of the aerobic and anaerobic test systems, <2 % of the applied radioactivity (AR) remained in the overlying waters with the rest partitioning into the sediment. Despite extraction using Ethanol, Tetrahydrofuran (THF) and Soluene, only a small proportion of the AR was extractable from the sediment (<17 % aerobic test system; <24 % anaerobic test system). Non extractable residues accounted for >74 % of the AR at Day 98 so it was not possible to establish degradation half-lives in the sediment and the total system, or to determine whether primary degradation had taken place.

No degradation products or extractable metabolites with concentrations of > 10 % of the AR were detected during the study.

No significant mineralization or volatile components were detected throughout the study.

Based on the data above, vandetanib is not predicted to be readily biodegradable during wastewater treatment, and therefore the phrase "Vandetanib is potentially persistent" is assigned.

## **Physical Chemistry Data**

Endpoint	Method	Test Conditions	Result	Reference
Solubility Water	OECD 105	30°C followed by 24 h @ 20°C	≥3200 mg/L @ pH 5 260 mg/L @ pH 7 1.2 mg/L @ pH 9	15
Partition Coefficient Octanol Water	OECD 107	-	LogD <sub>ow</sub> = -0.684 @ pH 3, 20°C LogD <sub>ow</sub> = 2.21 @ pH 7, 20°C LogD <sub>ow</sub> >3.9 @ pH 11, 20°C	16
Percentage Hydrolysis	OECD 111	-	<10 % @ pH 4, 7 & 9, 50°C	17
Hydrolysis Half-life			T <sub>1/2</sub> ≥1 yr (Estimated)	
Dissociation Constant	OECD 112	-	pKa = 5.14 (NH Group)	18
Dissociation Constant	Estimated using ACD Software for N with adjoining	-	pKa = 9.32	

Endpoint	Method	Test Conditions	Result	Reference
	methyl group			
Soil Adsorption Coefficient	OECD 121	-	Log K <sub>oc</sub> = 2.1 @ pH 1.0 Log K <sub>oc</sub> > 5.0 @ pH 11.5	19

Note 1: Results are expressed as mean measured concentrations

Note 2: The relevant endpoints measured were emergence, survival and growth

Note 3: Results are expressed as nominal concentrations

Note 4: Concentrations were confirmed by analysis, and results expressed as nominal

## Bioaccumulation

$\text{Log } D_{ow} = < 4$  at pH 7.

Vandetanib has no significant bioaccumulation potential, as indicated by the  $\text{Log } D_{ow}$ . Therefore the "statement" Vandetanib has low potential for bioaccumulation' is assigned.

## References

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