

## Fortum<sup>®</sup>

MR EF

### Sandoz AS

Pulver till injektions-/infusionsvätska, lösning 2 g  
(Vitt till gräddvitt pulver.)

Antibakteriella medel för systemiskt bruk, Cefalosporiner, tredje generationen.

### Aktiv substans:

Ceftazidim (vattenfritt)

### ATC-kod:

J01DD02

Läkemedel från Sandoz AS omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Miljöinformationen för ceftazidim (vattenfritt) är framtagen av företaget Pfizer för Ceftazidim Pfizer, Zavicefta

Miljörisk: Användning av ceftazidim (vattenfritt) har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Ceftazidim (vattenfritt) bryts ned i miljön.

Bioackumulering: Ceftazidim (vattenfritt) har låg potential att bioackumuleras.

### Detaljerad miljöinformation

Ceftazidime is highly soluble at environmentally relevant pH and is not expected to bioaccumulate, volatilise or adsorb to soils and sediments. It was not readily biodegradable, however evidence from the water sediment transformation test, in conjunction with the results of the definitive hydrolysis test, suggests that ceftazidime itself will not be persistent in the aquatic environment.

### Physical properties<sup>14</sup>

Solubility at pH 5: > 1000 mg/L

Solubility at pH 7: > 1000 mg/L

pKa: Non-ionizable

Vapor pressure:  $1.65 \times 10^{-10}$  mmHg

## Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.00268 \mu\text{g/L}$$

Where:

A =	19.53652604 kg (total sold amount API in Sweden year 2021) <sup>15</sup>
R =	0 % removal rate (worst case scenario)
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>3</sup>

LOEC (respiration inhibition) = > 1 000 000  $\mu\text{g/L}$

EC<sub>15</sub> (respiration inhibition) = 320 000  $\mu\text{g/L}$

*Green alga (Raphidocelis subcapitata) (guideline OECD 201)*<sup>4</sup>

LOEC 72 h (growth rate, chronic toxicity) = > 120 000  $\mu\text{g/L}$

NOEC 72 h (growth rate, chronic toxicity) = 120 000  $\mu\text{g/L}$

*Blue-green alga (Anabaena flos-aquae) (guideline OECD 201)*<sup>5</sup>

LOEC 72 h (growth rate, chronic toxicity) = 25  $\mu\text{g/L}$

NOEC 72 h (growth rate, chronic toxicity) = 13  $\mu\text{g/L}$

*Daphnids (Daphnia magna) (guideline OECD 211)*<sup>6</sup>

LOEC 21 days (reproduction, chronic toxicity) = > 9 200  $\mu\text{g/L}$

NOEC 21 days (reproduction, chronic toxicity) = 9 200  $\mu\text{g/L}$

*Fathead Minnow (Pimephales promelas) (guideline OECD 210)*<sup>7</sup>

LOEC 32 days (reproduction, chronic toxicity) = > 8 000  $\mu\text{g/L}$

NOEC 32 days (reproduction, chronic toxicity) = 8 000  $\mu\text{g/L}$

*Midge (Chironomus riparius) (guideline OECD 218)*<sup>8</sup>

LOEC 28 days (emergence, chronic toxicity) = > 100 000 µg/L

NOEC 28 days (emergence, chronic toxicity) = 100 000 µg/L

Based on the lowest NOEC for the species *Anabaena flos-aquae* and using the assessment factor<sup>2</sup> of 10, the PNEC is calculated to 13/10 = 1.3 µg/L

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

PEC/PNEC = 0.00268 / 1.3 = 0.00206, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase 'Use of ceftazidime has been considered to result in insignificant environmental risk.'

### **Degradation**

#### Biotic degradation

##### *Ready degradability*<sup>9</sup>

Test results have shown that the substance does not show properties of ready degradability (OECD 301B)

##### *Inherent degradability*<sup>10</sup>

Test results shows 65 % degradation in 14 days, i.e. the substance does not show properties of inherent degradability (guideline OECD 302B).

##### *Simulation studies*<sup>11</sup>

The degradation of [<sup>14</sup>C]ceftazidime in aquatic sediment systems was assessed according to the OECD 308 Test Guideline. Mineralisation was observed in both the high and low organic carbon test systems, reaching 3.9% and 31.2% (respectively) of the applied radioactivity by Day 93. Sediment samples were extracted twice using solvent mixes (3:1 and 1:1, v/v) of 0.05 M phosphate buffer (pH 3.4):methanol then a third extraction of 100% 0.05 M phosphate buffer. The extraction efficiencies of the radioactivity in the sediments were low, with a total of 8.8% and 7.1% of the total applied radioactivity being extracted from the high and low organic carbon test systems, respectively. Additional supplementary solvent extractions utilizing hexane, isopropanol, acetone, dimethylformamide and water were performed in sequence on the Day 29 high organic sediments which contained 51.6% of the applied dose following the initial extraction sequence. The total percentages of dosed radioactivity recovered were minimal, ranging between 0.0 to 2.4% of the applied radioactivity (AR). By Day 93, non-extractable residues measured in the high and low organic carbon sediments accounted for 42.3% and 13.4% of the applied radioactivity, respectively. Ceftazidime total system DT50 values in the high and low organic carbon sediment systems were 2.3 and 10 days, respectively. At the end of the 93-day long study, the active substance was no longer detectable in the low organic sediment, and only trace amounts (0.4%) were detected in the high organic sediment. Therefore, the substance is degraded in the environment.

#### Abiotic degradation

##### *Hydrolysis*<sup>12</sup>

Sterile freshwater hydrolysis half-life was measured according to guideline OECD 111.

Half-life (days)	pH	Temperature °C
20.6	5	25
1.3	5	50

0.5	5	60
18.0	7	25
0.9	7	50
0.3	7	60
1.5	9	25
0.4	9	35
0.1	9	50

#### *Justification of chosen degradation phrase*

Substance ceftazidime does not pass the test for readily degradable and inherent degradability. However, the simulation and hydrolysis studies show that the substance is degraded in the environment. Therefore, the phrase "*ceftazidime is degraded in the environment*" is chosen.

#### **Bioaccumulation**

##### *Partitioning coefficient<sup>13</sup>*

Log  $D_{ow}$  = -2.2 at pH 5 (guideline OECD 107)

Log  $D_{ow}$  = -2.21 at pH 7 (guideline OECD 107)

Log  $D_{ow}$  = -2.17 at pH 9 (guideline OECD 107)

#### *Justification of chosen bioaccumulation phrase*

Since log  $D_{ow}$  < 4 at pH 7, the substance 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. Study 120226/O: Ceftazidime: Activated sludge respiration inhibition test. Report No. BR0908/B. Brixham Environmental Laboratory, Brixham, UK. December 2013
4. Study 120226/C: Ceftazidime: Determination of toxicity to the green alga, *Pseudokirchneriella subcapitata*. Report No. BR0863/B. Brixham Environmental Laboratory, Brixham, UK. September 2013
5. Study 04-0169/C: Ceftazidime dihydrochloride: Toxicity to the blue green alga, *Anabaena flos-aquae*. Report No. BL7723/B. Brixham Environmental Laboratory, Brixham, UK. December 2004
6. Study 120226/D: Ceftazidime: Determination of effects on reproduction to *Daphnia magna*. Report No. BR0890/B. Brixham Environmental Laboratory, Brixham, UK. February 2014
7. Study 120226/E: Ceftazidime: Determination of effects on the early life-stage of the fathead minnow (*Pimephales promelas*). Report No. BR0866/B. Brixham Environmental Laboratory, Brixham, UK. September 2013
8. Study 120226/N: Ceftazidime: Determination of effects in sediment on emergence of the midge, *Chironomus riparius*. Report No BR0917/B. Brixham Environmental Laboratory, Brixham, UK. February 2014
9. Study 120226/G: [14C] Ceftazidime: Determination of ready biodegradability. Report No. BR0894/B. Brixham Environmental Laboratory, Brixham, UK. April 2014.
10. Study 04-0169/F

- 11.** Study 2573W: Ceftazidime: Aerobic transformation in aquatic sediment systems. Project No. 2573W. PTLR West, Hercules, California, USA. January 2015
- 12.** Study 11-0014/A: Ceftazidime: Hydrolysis as a function of pH. Report No. BR0665/B. Brixham Environmental Laboratory, Brixham, UK. April 2014
- 13.** Study 120226/B: Ceftazidime: Partition coefficient (n-octanol/water): Shake flask method. Report No. BR0870/B. Brixham Environmental Laboratory, Brixham, UK. October 2013.
- 14.** Study 120226/A: Ceftazidime: Determination of water solubility. Report No. BR0869/B. Brixham Environmental Laboratory, Brixham, UK. August 2013
- 15.** IQVIA KG Consumption 2021 report.