FASS

Dasatinib Sandoz

M ℞ (F)

Sandoz AS

Filmdragerad tablett 50 mg

(Vit till benvit, bikonvex, oval filmdragerad tablett med ”50” präglat på den ena sidan och slät på den andra sidan och med dimensionerna 10,9 mm x 5,8 mm.)

Övriga antineoplastiska medel, proteinkinashämmare.

Aktiv substans:

Dasatinib (vattenfri)

ATC-kod:

L01EA02

Läkemedel från Sandoz AS omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för dasatinib (vattenfri) är framtagen av företaget Bristol-Myers Squibb för SPRYCEL, Sprycel

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

Nedbrytning: Dasatinib bryts ned långsamt i miljön.

Bioackumulering: Dasatinib har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

The PEC is calculated according to the following formula:

Equation

$$PEC\ (\mu g/L) = \frac{A \times 1000000000 \times (100-R)}{365 \times P \times V \times D \times 100} = 1.5 \times 10^{-6} \times A \times (100-R)$$

It is based on the following data:

A = 7.8194 kg (sales data for 2021 obtained from IQVIA/LIF; includes 0.9656 kg for dasatinibmonohydrate and 6.8538 kg for dasatinib (vattenfri))
R = 0 (conservative estimate)
P = number of inhabitants in Sweden = 10×10^6
V (L/day) = volume of wastewater per capita and day = 200 (Ref. 11)
D = factor for dilution of waste water by surface water flow = 10 (Ref. 11)

PEC = $1.37 \times 10^{-6} \times A \times (100-R)$

$PEC = 1.37 \times 10^{-6} \times 7.8194 \times (100-0)$

PEC = 0.001 µg/L

Excretion (metabolism):

After human ingestion, dasatinib is extensively metabolized[1]. Elimination is primarily via the feces. Following a single oral dose of [14C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites. No removal (R=0) is used as a worst case scenario for the PEC calculation above.

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Activated Sludge (OECD 209) [2]

EC_{50} > 1000 mg/L (highest dose tested)
NOEC = 1000 mg/L (highest dose tested)

Algae (*Pseudokirchneriella subcapitata*) (OECD 201)[3]

EC_{50} 72 h (growth rate) > 0.18 mg/L (highest dose tested)
NOEC 72 h (growth rate) = 0.073 mg/L

Crustacean (*Daphnia magna*)

Chronic Toxicity (OECD 211)[4]

NOEC 21 days (mean number of offspring per female) = 0.068 mg/L
NOEC 21 days (survival/growth) = 0.17 mg/L

Fish (Fathead Minnow; *Pimephales promelas*)

Chronic Toxicity (OECD 210)[5]

NOEC 28 days (Larval Survival) = 0.018 mg/L
LOEC 28 days (Larval Survival) = 0.034 mg/L
No effects were observed on other endpoints.

Environmental Risk Classification (PEC/PNEC Ratio)

The PNEC for aquatic organisms is based on the lowest NOEC of 0.018 mg/L (18 µg/L), noted in the fish chronic toxicity study. An assessment factor of 10 is applied to the ecotoxicity base set of three chronic studies.

$PNEC_{aquatic}$ = 18 / 10 = 1.8 µg/L

The PEC/PNEC calculation below for the aquatic compartment is less than 0.1 which justifies the phrase “Use of dasatinib has been considered to result in insignificant environmental risk”

$PEC/ PNEC_{aquatic} = 0.001 / 1.8$

$= 5.55 \times 10^{-4}$

The PNEC for microorganisms is based on the NOEC of 1,000 mg/L in the Activated Sludge Respiration Inhibition test, OECD 209. An assessment factor of 10 is applied.

$PNEC_{microorganism} = 1000 / 10 = 100$ mg/L = 100000 µg/L

Note the $PEC_{microorganism}$ for assessing exposure to waste treatment microorganisms is considered ten-fold higher than for surface wasters due to the assumption of a ten-fold dilution when released from waste water treatment facilities.

$PEC_{microorganism} / PNEC_{microorganism} = 0.01 / 100000$

$= 1.0 \times 10^{-7}$

The PEC/PNEC calculation below for the microorganism is less than 0.1 and therefore the use of dasatinib has been considered to result in insignificant environmental risk to microorganisms.

Degradation

Biotic Degradation

Inherent Degradability (OECD 302A)[6]:

Dasatinib undergoes primary biodegradation with a half-life of 5.4 hours but is not readily biodegradable. It exhibited less than 1%

mineralization to $^{14}CO_2$ at day 21. HPLC/RAM analysis showed the conversion of dasatinib to a series of metabolites that persisted through day 21 of the study, the final sampling interval.

Simulation Studies (OECD 308)[7]:

The fate of dasatinib was studied in two natural aquatic sediment systems. The sediment from Taunton River (Sediment 1) was a fine textured loam with a slightly acidic pH and high organic carbon content (2.9% w/w dry weight), while that from the Weweantic River (Sediment 2) was a coarse textured, slightly acidic sand with a lower organic carbon content(0.88% w/w dry weight). In both aerobic sediment systems dasatinib declined in the water phase over time (not detected at day 101) and increased in the sediment phase (38.7-54.8% of initial radioactivity after 101 days). Several peaks that were presumed to be degradation products of dasatinib were noted but none reached 10% of the administered dose and were not analyzed any further.
A small amount of material did degrade completely as noted by the 1.7 and 0.9% CO_2 evolution in the two systems. The total system half-life of dasatinib (based on dissipation rates) for sediments 1 and 2 was 79.7 and 131 days, respectively. The half-life in water was 3.5 and 4 days in sediments 1 and 2, respectively. Total recoveries of radioactivity (mass balances) for sediments 1 and 2 were 98.9% and 98.5 % of the amounts initially applied, respectively. In both aquatic sediments, evolution of volatile radioactivity was minimal (<0.1% applied radioactivity after 101 days). Non-extractable radioactivity in the sediment (sediment-bound residue) accounted for 56.3% and 27.1% in sediments 1 and 2, respectively. Extractions were performed using

a shaker table at 200 rpm for 10 minutes with acetonitrile:water: trifluoroacetic acid (80:20:0.1% by volume) and acetonitrile:water: trifluoroacetic acid (2 times; 80:20:0.5 % by volume). Additional extractions were performed on the Day 101 post extraction solid samples using methanol, ethyl acetate and hexane. These harsh extraction solvents were used in attempt to remove any additional bound-sediment residue. These extraction procedures were deemed to be suitable.

Abiotic Degradation

Photolysis (FDA 3.10)[8]:

The experimental half-life of dasatinib) at 2.15 mg/L was measured to be 3.14, 2.18 and 1.33 hours at pH 5, 7 and 9 respectively. The environmentally relevant photolytic half-life of dasatinib using the direct photoreaction rate constant, kpe, was determined to be 3.17, 2.21 and 1.35 hours at pH 5, 7 and 9, respectively. Based on these results, dasatinib is expected to photolyze rapidly in those areas of natural water bodies receiving sunlight.

Based on the OECD 302A study, dasatinib is not readily biodegradable. However based on the DT_{50}s determined in the OECD 308 study and the 2012 FASS guidance for pharmaceutical companies, the phrase “dasatinib is slowly degraded in the environment” is justified.

Bioaccumulation

Partitioning Coefficient (OECD 107)[9]:

Dasatinib has log Kow values of 1.85 at pH 5, 3.56 at pH 7.8 and 3.56 at pH 9.

Bioaccumulation Factor (OECD 305) [10]:

The kinetic bioaccumulation factor (BCF; total residue) tested at 2 concentrations was <5.

Justification of chosen bioaccumulation phrase:

Since the BCF is <500, the phrase “dasatinib” has low potential for bioaccumulation” is justified.

PBT/vPvB Assessment

Dasatinib does not meet the criteria to be considered a PBT or vPvB substance.

References

1. Bristol-Myers Squibb. United States Prescribing Information for Sprycel. Available at: https://packageinserts.bms.com/pi/pi_sprycel.pdf. Revised September 2016.

2. Springborn Laboratories Inc., Study No. 12534.6279, Src Kinase (BMS-354825-03) – Determination of Activated Sludge Respiration Inhibition (OECD 209), 2005.

3. Springborn Laboratories Inc., Study No. 12534.6277, Src Kinase (BMS-354825-03) - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella subcapitata (OECD 201), 2005.

4. Springborn Laboratories Inc., Study No. 12534.6278, Src Kinase (BMS-354825-03) - Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static-Renewal Conditions (OECD 211), 2005.

5. Springborn Smithers Laboratories, Study No. 12534.6360, Dasatinib – Early Life-Stage Toxicity Test with Fathead Minnow, *Pimephales promelas*, Following OECD Guideline 210, 2010.

6. Springborn Laboratories Inc., Study No. 12534.6280, [14C]Src Kinase (BMS-354825-08) – Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test (OECD 302A), 2005.

7. Springborn Smithers Laboratories, Study No. 12534.6362, [14C]Dasatinib (BMS 354825-08) - Aerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308, 2010.

8. Springborn Laboratories Inc., Study No. 12534.6283, [14C]Src Kinase (BMS-354825-08) – Determination of Photodegradation in Water (FDA 31.0), 2005.

9. Springborn Laboratories Inc., Study No. 12534.6282, Src Kinase (BMS-354825-03) - Determination of the n-Octanol/Water Partition Coefficient (OECD 107) 2005.

10. Springborn Smithers Laboratories, Study No. 12534.6365, Dasatinib - Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (*Lepomis macrochirus*) Following OECD Guideline 305, 2010.

11. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/informa requirements_en.htm