

CRIXIVAN[®]**M R F_f****MSD**

Kapsel, hård 400 mg

(Tillhandahålls för närvarande ej) (vit, halvgenomskinlig, märkt CRIXIVAN 400 mg med grön text)

Virushämmande medel

Aktiv substans:

Indinavir

ATC-kod:

J05AE02

Läkemedel från MSD omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Indinavir

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

Nedbrytning: Indinavir är potentiellt persistent.

Bioackumulering: Indinavir har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = \frac{(A \cdot 10^9 \cdot (100 - R))}{(365 \cdot P \cdot V \cdot D \cdot 100)} = 1.5 \cdot 10^{-6} \cdot A(100 - R)$$

$$\text{PEC} = 0 \mu\text{g/L}$$

Where:

A = 0 kg (total sold amount API in Sweden year 2015, data from IMS Health).

R = 0 % removal rate (worst case assumption)

P = number of inhabitants in Sweden = $9 \cdot 10^6$

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

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

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Selenastrum capricornutum) (USFDA 4.01) (Reference II):

NOEC (10 day) (cell number) = 6470 $\mu\text{g/L}$

MIC = 12800 $\mu\text{g/L}$

Inhibition of growth is the preferred end-point for calculation of the PNEC, but as EC_{50} could not be determined for growth rate and the yield end-point in this case gives a more protective PNEC, the yield end-point was used.

Crustacean, water flea (Daphnia magna):

Acute toxicity

EC₅₀ 48 h (mortality) >20000 µg/L (USFDA 4.08) (Ref. III)

Fish, fathead minnow (Pimephales promelas):

Acute toxicity

EC₅₀ 96 h (mortality) >20000 µg/L (USFDA 4.11) (Ref. III)

Fish, rainbow trout (Oncorhynchus mykiss):

Acute toxicity

EC₅₀ 96 h (mortality) 438000 µg/L (USFDA 4.11) (Ref. IV)

PNEC = 6.5 µg/L (6470 µg/L/ 1000 based on the most sensitive NOEC for the algae and an assessment factor (AF) of 1000)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0/6.5 = 0, i.e. PEC/PNEC ≤ .1 which justifies the phrase "Use of indinavir has been considered to result in insignificant environmental risk"

Degradation

Biotic degradation

Biodegradation Simulation Screening

Test results 81%, degradation (loss of parent) in 28 days in wastewater effluent. Degradation products, identified via HPLC were more polar than the parent. No metabolite was definitively identified. (US FDA 3.11) (Ref. V)

Abiotic degradation

Hydrolysis:

No significant degradation ($t_{1/2}$ @ pH 7 = 651 days) (USFDA 3.09) (Ref.VI)

Photolysis:

Test results 70% degradation in 42 hrs (US FDA 3.10). (Ref.VII)

Justification of chosen degradation phrase:

Indinavir does not pass the ready biodegradation test but is degradable in acclimated biological systems. As no data are available on the toxicity of the metabolites, the phrase “Indinavir is potentially persistent” is thus chosen.

Bioaccumulation

Partitioning coefficient:

$\log D_{ow} = -2.66$ at pH 7 (OECD 117). (Ref.III)

Justification of chosen bioaccumulation phrase:

Since $\log D_{ow} < 4$ at pH 7, the substance has low potential for bioaccumulation

References

- I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_
- II. Toxikon Environmental Sciences, 1995. “MK-0639: Toxicity to the Freshwater Green Alga, *Selenastrum capricornutum*, Under Static Test Conditions”, 12 May, 1995.
- III. Merck, 1995. “Ecotoxicological Characterization of HIV Protease Inhibitor, MK-0639, Merck Research Laboratories, 22 June 1995.

IV. Toxikon Environmental Sciences, 1995. "MK-0639: Acute Toxicity to Rainbow Trout, *Oncorhynchus mykiss*, under Static Test Conditions", 8 May, 1995.

V. Toxikon Environmental Sciences, 1995. "MK-0639: Biodegradation Inoculum Source Screening", 8 December, 1995.

VI. Toxikon Environmental Sciences, 1995. "MK-0639: Determination of the Rate of Hydrolysis as a Function of pH at 25oC", 29 March, 1995.

VII. Toxikon Environmental Sciences, 1995. "MK-0639: Determination of Aqueous Photolysis", 9 August, 1995.