FASS

Ultravist®

Bayer

Injektions-/infusionsvätska, lösning 240 mg I/ml
(Tillhandahålls ej) (klar, färglös till svagt gul lösning)

Röntgenkontrastmedel för intravaskulär användning

Aktiv substans:
Jopromid

ATC-kod:
V08AB05

Läkemedel från Bayer omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Jopromid

Miljörisk: Användning av jopromid har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Jopromid är potentiellt persistent.
Bioackumulering: Jopromid har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^9*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}$ *A*(100-R) = 0.00508 µg/L

Where:

A = 37.09 kg (total sold amount API in Sweden year 2021, data from IQVIA / LIF)

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available

P = number of inhabitants in Sweden = $10 *10^6$

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

D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Reference I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

*Algae (*green algae*, Desmodesmus subspicatus):*

NOEC 72 hours (growth rate) ≥ 10.000 mg/L, E_rC_{50} 72 h (growth rate) > 10.000 mg/L. Guideline OECD 201. (Reference II)

*Crustacean (*waterflea, *Daphnia magna):*

Acute toxicity

EC_{50} 48 hours (immobilization) ≥ 10.000 mg/L. Guideline OECD 202. (Reference III)

Chronic toxicity

NOEC 21 days (reproduction) ≥ 10.000 mg/L. Guideline OECD 211. (Reference IV)

*Fish (*zebrafish, *Danio rerio):*

Acute toxicity

LC_{50} 48 hours (survival) ≥ 10.000 mg/L. Guideline OECD 203.

(Reference V)

Micro-organisms (*Pseudomonas putida*)

EC_{10} 16 hours (cell proliferation) ≥ 1.000 mg/L. DIN38412 L8.

(Reference VI)

The PNEC was calculated based on the acute aquatic toxicity data since there was insufficient chronic aquatic toxicity data. The PNEC was calculated by division of the lowest effect level (EC_{50} or LC_{50}) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). In the case of iopromide, there was no effect with algae, crustacean, or fish up to the highest test concentration of 10.000 mg/L, i.e., none of the taxa was more sensitive than others. The lowest effect level to be considered was therefore EC_{50} and LC_{50} ≥ 10.000 mg/L. The regulatory default standard AF of 1.000 was used, which is applicable when there are acute aquatic toxicity studies representing the three trophic levels (algae, crustacean, and fish).

PNEC = 10.000 mg/L / 1.000 = 10 mg/L = 10.000 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.00508 µg/L / 10.000 µg/L = 0.000000508 = $5.08x10^{-7}$.

Justification of chosen environmental risk phrase:

A risk quotient far below 0.1 for iopromide qualifies for the phrase “Use of iopromide has been considered to result in insignificant environmental risk”.

Degradation

Biotic degradation

Ready degradability:

The ready biodegradability of iopromide was assessed in an OECD screening test with municipal sewage sludge. The test item concentration was 20 mg/L as DOC. Aniline was used as positive control and attained 16 % and 93 % biodegradation after 3 and 8 days. All validity criteria were met. The study reported 0 % biodegradation of iopromide in 28 days. Guideline OECD 301E. (Reference VII)

Inherent degradability:

Inherent biodegradation was determined in a study according to OECD 302B with activated sludge from a municipal sewage treatment plant, over a prolonged period of 42 days (standard test duration 28 days). Iopromide concentration corresponded to 100 mg/L DOC in duplicate. Degradation of test and control item was determined by DOC analysis.

The study reported 23 % biodegradation in 28 days, which is below the threshold of 70 % and therefore iopromide is not considered inherently biodegradable. Guideline OECD 302B. (Reference VIII)

Simulation studies:

The degradation of iopromide was investigated in a LSSTP simulating a municipal sewage treatment. The mean DOC of the synthetic sewage influent was 60.3 mg/L. The median of DOC degradation of the synthetic sewage was 88.5 %, 90.5 %, 88.4 % and 85.1 % in the control plant, 0.1, 1 and the 100 mg/L iopromide-dosed plant, respectively, thus passing the quality criterion for a stable run according to OECD guideline No. 303A. The additional monitored parameters (content of dry substance in the sludge, the sludge settling behaviour and nitrification) did not

differ between control and dosed plants and do therefore not point towards an inhibitory effect of iopromide on the sludge biocoenosis.

Samples were analyzed by HPLC-UV and samples taken at the end of the study used HPLC-ICP/MS and LA/ICP/MS to determined total iodine content and degradation products. Analytical recovery of iopromide from LSSTP effluent from the control plant spiked with standard material (0.1, 0.5 and 1.0 mg iopromide diluted in 10 mL sewage, three replicates) was above 94 % (standard deviation < 6 %) at all three concentrations, indicating that the chosen extraction method yielded almost quantitative recovery.
With the onset of iopromide elimination one metabolite appeared in the effluent of all LSSTPs. This metabolite was identified as rac-5-amino-N,N0-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-ethylisophtl (CAS No. 154361-51-0) and represents a cleavage product of a side chain of iopromide resulting in the free amine of the parent.

Iopromide was eliminated to more than 80 % in the 100 mg/L concentration after a lag period of 31 days The average degree in the plateau phase was 100 %. In the LSSTP incubated with 1 mg/L iopromide elimination reached more than 80 % after 38 days. The average degree in the plateau phase was 96 %. At the lowest concentration (0.1 mg/L) the average degradation degree during the plateau phase was only 1 %. (Reference IX)

Abiotic degradation

Hydrolysis:
This study reported that iopromide was stable at 50 °C and pH 5, 7, and 9. Guideline FDA TAD 3.09. (Reference X)

Justification of chosen degradation phrase:
Iopromide is not readily biodegradable and resistant to hydrolysis, which qualifies for the phrase “Iopromide is potentially persistent”.

Bioaccumulation

Partitioning coefficient:
The log D_{ow} was determined in a shake-flask method study. The log D_{ow} was reported as -2.33. Guideline FDA TAD 3.02. (Reference IX)

Justification of chosen bioaccumulation phrase:
As the log D_{ow} was well below 4 iopromide is not considered bioaccumulative which qualifies for the phrase “Iopromide has low potential for bioaccumulation”.

References

I. Guidance on information requirements and Chemical Safety Assessment Chapter R.16: Environmental exposure assessment. V3.0, Feb. 2016.
II. Toxicity of iopromid (ZK 35.760) to the freshwater alga *Scenedesmus subspicatus*. Schering AG, Experimental Toxicology, Report no. A771, Study no. TX93084 (Akzo Research laboratories CRL F93082)
III. Acute immobilization test of iopromide with *Daphnia magna*. Schering AG, Experimental Toxicology, Report no. A781, Study no. TX93202
IV. Chronic reproduction study of iopromide on *Daphnia magna*. Schering AG, Experimental Toxicology, Report no. A767, Study no. TX93041

V. Acute toxicity of iopromide to the Zebra fish *Brachydanio rerio*. Schering AG, Experimental Toxicology, Report no. A586, Study no. TX92380

VI. Growth inhibition test of Iopromide on the bacterium *Pseudomonas putida*. Schering AG, Experimental Toxicology, Report no. 9155, Study no. TX90153

VII. Study on the biodegradability of Meglumin amidotrizoate, Iohexol and Iopromide according to the modified OECD Screening Test. Schering AG, Experimental Toxicology, Report no. 9170, Study no. TX90105

VIII. Study on the inherent biodegradability of iopromide in the Zahn-Wellens-Test. Schering AG, Berlin. Experimental Toxicology. Report no. X353.

IX. Elimination of iopromide in a laboratory scale waste water treatment plant with activated sludge. Schering AG, Experimental Toxicology, Report no. A30064, Studyno. TX19550122.

X. The rate of hydrolysis of lopromide Injection, (Ultravlst® Injection) (Iopromide: ZK 35 760). Schering AG, Berlin. Institute for physico-chemistry. Report no. KT48, study no. NSR_92_119.

XI. The n-octanol/water partition coefficient of iopromide injection (Iopromide, ZK 35 760). Schering AG, Berlin, Institute for physico-chemistry. Report no. KT49, study no. NSR_91_138.