FASS

Magnevist®

Bayer

Injektionsvätska, lösning 0,5 mmol/ml

Avregistreringsdatum: 2018-11-30 (Tillhandahålls ej) (Klar, färglös till svagt gul lösning)

Paramagnetiskt kontrastmedel för magnetisk resonanstomografi (MRT)

Aktiv substans:

Gadopentetatdimeglumin

ATC-kod:

V08CA01

För information om det avregistrerade läkemedlet omfattas av Läkemedelsförsäkringen, kontakta Läkemedelsförsäkringen.

Läs mer om avregistrerade läkemedel

Miljöpåverkan

Gadopentetatdimeglumin

Miljörisk: Användning av gadopentetatdimeglumin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Gadopentetatdimeglumin är potentiellt persistent.
Bioackumulering: Gadopentetatdimeglumin 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) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A*(100-R) = 9.59*10^{-7}$ µg/L

Where:
A = 0,007 kg (total sold amount API in Sweden year 2022, 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) > 100 µg/L, E_rC_{50} hours (growth rate) ≥ 100 µg/L. Guideline OECD 201.
(Reference II)

*Crustacean (*waterflea, *Daphnia magna):*
Acute toxicity
EC_{50} 48 hours (immobilization) ≥ 100 µg/L. Guideline OECD 202. (Reference III)
Chronic toxicity
NOEC 21 days (reproduction) ≥ 10 µg/L. Guideline OECD 211. (Reference IV)

*Fish (*zebrafish, *Danio rerio):*
Acute toxicity
LC_{50} 96 hours (survival) ≥ 100 µg/L. Guideline OECD 203. (Reference V)

Microorganisms (Pseudomonas putida):
EC_{10} 16 hours (growth inhibition) ≥ 100 µg/L. Guideline DIN38412 L8. (Reference VI)

The PNEC was calculated based on the chronic aquatic toxicity data. The PNEC was calculated by division of the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). While there was no effect with any taxon the PNEC was derived considering the lowest test concentration of the daphnids, which was 10 µg/L. The regulatory default standard AF of 10 was used, which is applicable when there are chronic aquatic toxicity studies representing the three trophic levels (algae, crustaceans, and fish).

PNEC = 10 µg/L / 10 = 1 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with $9.59*10^{-7}$ µg/L / 1 µg/L = $9.59*10^{-7}$.

Justification of chosen environmental risk phrase:
A risk quotient of ≤ 0.1 qualifies for the phrase “Use of Gadopentetate dimeglumine has been considered to result in insignificant environmental risk.”.

Degradation

Biotic degradation

Ready degradability:
Biodegradability of gadopentetate dimeglumine was determined in a study according to the test method OECD 301E with GLP documentation. This test item consists of the acid diethylenetriamine penta-acetic acid (DTPA) which binds 1 atom of gadolinium (Gd) and two molecules of methylglucamine (dimeglumine). The microbial community (activated sludge form a municipal sewage treatment plant) was exposed to 20 mg/L DOC (corresponding to 54 mg/L test item), a positive control (sodium acetate), and a control all in duplicates. Ready biodegradability was determined as decreasing DOC in the test solutions. The study was

extended to 62 days as a slight degradation was observed towards the end of the standard exposure duration of 28 days. Next to DOC specific chemical analysis of the Gd-DTPA complex by HPLC/VU was conducted.

The reference substance was degraded by 90 % on day 3 and 95 % on day 14. Chemical analysis revealed no degradation of the Gd-DTPA complex while DOC analysis revealed a ready biodegradation of 25 % at day 28 and 45 % at day 62.

However, the observed biodegradation was considered to be referred to the dimeglumine fraction only. Dimeglumine provides 2 * 7 = 14 carbon atoms of a total of 28 carbon atoms of the gadopentetate dimeglumine, wherefore 50 % biodegradation can be expected to be based on dimeglumine. In addition, the chemical analysis revealed that the Gd-DTPA complex remained stable. Hence, the Gd-DTPA complex was considered to be not readily biodegradable, i.e., revealed 0 % biodegradation after 62 days. Guideline OECD 301. (Reference VII)

Simulation studies:
Transformation of gadopentetate dimeglumine was determined in a water-sediment study according to OECD 308 (aerobic part). The test substance was incubated in an aerated system, which contained intact lake sediment and overlaying lake water. The substance was incubated over a period of 100 days. Because of the high hydrophilicity of the test substance and the expected low adsorption the organic carbon content and the grain size of the sediment were assumed to have no influence on the sorption process. Therefore, only one type of sediment was used. The concentration of the test item in the filtered overlaying water was analyzed by HPLC/UV. Additionally, the content of Gadolinium (Gd) in sediment and the filtrates of the overlaying water, the filtrates of demineralized water and the filtrates of diluted HCl were analyzed by ICP/MS, in order to recover all sediment related, dissolved substance. Gadopentetate dimeglumine was only marginally removed from the overlaying water after 100 days in the water-sediment system. Gd was found to a low extent in the sediment taken at the beginning, as well as after 2, 8, and 15 days. Because Gd was detected also in the non-dosed sediment, it is likely, that the Gd determined in the sediment at day 2, 8, and 15 is of geogenic origin. The test solution was not completely removed during filtration, wherefore it is possible that little amounts of Gd in the sediment resulted from that solution. At the end of the incubation, there was a slight increase of the Gd concentration in the sediment that was supposed to be related to the introduced substance.

This study reported no transformation of gadopentetate dimeglumine in and no DT_{50} could be derived, wherefore it is considered to be > 120 days. Guideline OECD 308. (Reference VIII)

Justification of chosen degradation phrase:
Since no DT_{50} could be derived this is considered to be > 120 d for the total system, which qualifies for the phrase “Gadopentetate dimeglumine is potentially persistent.”.

Bioaccumulation
Partitioning coefficient:
The n-octanol/water partition coefficient log D_{OW} of gadopentetate dimeglumine was determined according to test method FDA TAD no. 3.02. The log D_{ow} was reported with -5.4 at pH 7 and 25 °C. Guideline Shake flask method, FDA TAD 3.02. (Reference IX)

Justification of chosen bioaccumulation phrase:
As the log D_{ow} was < 4 gadopentetate dimeglumine is not considered bioaccumulative which qualifies for the phrase “Gadopentetate dimeglumine 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. Growth inhibition test of Magnevist® (Dimeglumine gadopentetate, ZK 93035/dimegl.) on the green algae *Desmodesmus subspicatus*. Nonclinical Drug Safety, Bayer Schering Pharma AG, Report no. A34544, Study no. TXST20060212.

III. Acute immobilization test of Magnevist® (ZK 93035) with *Daphnia magna*. Nonclinical Drug Safety, Bayer Schering Pharma AG, Report no. A34543, Study no. TXST20060211.

IV. Reproduction study of Magnevist® (ZK 93035) in *Daphnia magna*. Nonclinical Drug Safety, Bayer Schering Pharma AG, Report no. A30908, Study no. TXST20050336.

V. Acute toxicity of Magnevist ® (dimeglumine gadopentetate, ZK 93035/dimegl.) to the Zebra fish *Danio rerio*. Nonclinical Drug Safety, Bayer Schering Pharma AG, Report no. A29951, Study no. TXST20050264.

VI. Growth inhibition test of dimeglumine gadopentetate on the bacterium *Pseudomonas putida*. Schering AG, Experimental Toxicology, Report no. 9199, Study no. TX19900197.

VII. Study on the of dimeglumine gadopentetate according to the modified OECD screening test. Schering AG, Experimental Toxicology, Report no. A31214, Study no. TXST1990262.

VIII. Aquatic-sediment study (aerobic) with Magnevist® (dimeglumine biodegradability gadopentetate, ZK 93035/dimegl.). Nonclinical Drug Safety, Bayer Schering Pharma AG, Report no. 37066, Study no. TXST20070034 (2007)

IX. The octanol/water partition coefficient of gadopentetatetic acid, dimegl. (ZK 93035) at pH = 7 and 25 ºC. Schering AG, General Physical Chemistry, Report no. KS25, Study no. 94/137.