FASS

Mifegyne

MRx EF

Nordic Drugs

Tablett 200 mg

(ljusgula, cylindriska, bikonvexa tabletter.)

Progesteronhämmare

Aktiv substans:

Mifepriston

ATC-kod:

G03XB01

Läkemedel från Nordic Drugs omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Mifepriston

Miljörisk: Användning av mifepriston har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Mifepriston bryts ned i miljön.
Bioackumulering: Mifepriston 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)

PEC = 0.0005686 µg/L

Where:

A = 4.15 kg (total sold amount API in Sweden year 2020[1], data from IQVIA).

R = 0 % removal rate. This is considered a conservative value.

P = number of inhabitants in Sweden = $10*10^{6}$ [2]

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (Ref. 1)

D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Ref. 1)

Predicted No Effect Concentration (PNEC)

Calculation of PNEC is obtained by applying assessment factors (AF) to long-term ecotoxicity data:[3]

Lowest NOEC/AF

PNEC = 0.01 µg/L

Where:

Lowest NOEC = 0.1 µg/L (Fish (*Danio rerio*), full life cycle study).

AF = 10 based on the availability of chronic toxicity studies for three trophic levels.

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[1] Most recent data for Sweden.

[2] According to *Environmental classification of pharmaceuticals www.fass.se. Guidance for pharmaceutical companies* (2012 v3.0)

[3] Guidance on information requirements and chemical safety assessment Chapter R10 (ECHA, 2008)

Ecotoxicological studies

Algae (*Pseudokirchneriella subcapitata)* (OECD 201) (Ref. 2):
EC_{50} 72 h (growth inhibition) >746 µg/L
NOEC 72 h (growth inhibition) ≥ 746 µg/L
(Limit of solubility)

Crustacean (Daphnia magna):
Chronic toxicity (OECD 211) (Ref. 3)
EC50 21 d (reproduction) >985 µg/L
NOEC 21 d (reproduction) = 985 µg/L
(Limit of solubility)

Microorganisms (activated sludge)
Respiration inhibition test (OECD 209) (Ref. 4)
NOEC > 100 mg/L (nominal)

Fish (Danio rerio)
Fish full life cycle study (Ref. 5)
NOEC = 100 ng/L (nominal).

The purpose of this fish full life cycle study was the assessment of effects of Mifepristone on different life stages of zebrafish (*Danio* rerio) and was mainly following the recommendations by the OECD draft Test Guideline ZEOGRT (Zebrafish Extended One Generation Test, 2018).[4]
Fertilised zebrafish eggs were exposed in a flow-through test to aqueous test media containing the test item at various concentrations under defined conditions. The test lasted for 29

weeks. The recorded endpoints were mortality and behaviour during all investigated life stages, hatching success of larvae and juvenile growth. This study encompassed 5 treatment groups (3 concentrations of the test item, a negative control, and a solvent control) with 4 replicates each. The test concentrations were 1.00, 10.0 and 100 ng/L each in 20 µL DMF/L, corresponding to the following overall time-weighted arithmetic mean measured concentrations: 1.24, 11.1 and 89.4 ng test item/L.

No systemic toxicity was observed in this study. NOEC can therefore be defined at the highest concentration tested (100 ng/L, nominal concentration).

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[4] In addition, the following guidelines were also taken into account when defining the study design: EPA Guideline 712-C-96-122: OPPTS 850.1500, “Fish life cycle toxicity” April 1996; ECD Series on Testing and Assessment, No. 23, "Guidance Document on Aqueousphase Aquatic Toxicity Testing of Difficult Test Chemicals", 2nd Ed., February 08, 2019; OECD TG 240: Draft guideline on the Zebrafish Extended One Generation Reproduction Test (ZEOGR); SANCO/3029/99 rev.4 11/07/00: Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A; Section 4) and Annex III (PART a; Section 5) of Directive 91/414

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.0005686 /0.01 = 0.05686, i.e., PEC/PNEC ≤ 0.1 which justifies the phrase “Mifepristone has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready biodegradability (OECD 301F):

In an aerobic biodegradation study (28 days) in water Mifepristone was not considered as readily biodegradable (<10% degradation) (Ref. 6).

Inherent degradability:

No data on inherent degradability.

Aerobic transformation in aquatic sediment systems (OECD 308):

Evidence from the OECD 308 study suggests that Mifepristone is degraded in the environment (Ref. 7). Mifepristone was exposed to two aerobic biologically active sediment systems (sediment A and sediment B).[5] The degradation rate of the test item and its major transformation products, mass balance and transformation product pattern were determined. In addition, major unknown transformation products were identified and the DT50 and DT90 (time when 50 % or 90 % of the compound disappears, respectively) values were calculated.

Where feasible, transformation rate was determined for the whole sediment system and for the water and sediment compartment separately.

The transformation rates of the test item were determined in two different sediment systems. Sediment system samples were incubated, and samples were taken at specific time points. Extractable radioactivity, non-extractable residues and volatile transformation products were investigated. Selected extraction solvent mixture was acetonitrile/H_2O (80:20) + 0.5 % formic acid.

Parent substance and known transformation product

characterisation in the water phase and sediment extracts were done by co-chromatography using HPLC with radio detection. The results show a transition of the test item from the water phase to the sediment phase and its degradation. At test start, Mifepristone could only be detected in the water phase. In sediment A the amount in the water phase decreased to 3.9% AR (applied radioactivity) at day 14 and was below the limit of detection until the end of the study. In sediment B the amount in the water phase decreased to 21.0% AR at day 14 and 5.5% AR at day 56 and was below the limit of detection at day 23 and at day 100.

The extractable amount from the sediment phase was below the detection limit at start of the study. It increased reaching a maximum of 47.9% AR at day 7 (sediment A) or 29.5 % AR at day 7 (sediment B). At the end of the study (day 100) the amounts were 21.2% of AR (sediment A) and 6.0% of AR (sediment B).

For the total system, a decrease of the amounts of Mifepristone was observed. In sediment A, it decreased from 96.6 % AR (day 0) to 21.2 % AR (day 100) and in sediment B from 96.8 % AR (day 0) to 6 % AR (day 100). The DT50/DT90 values for Mifepristone are 4.5/14.9 days (water phase), 72.1/239.0 days (sediment phase) and 14.3/212.0 days (total system) for sediment system A and 4.1/13.5 days (water phase), 29.6/98.4 days (sediment phase) and 12.7/42.3 days (total system) for sediment system B.

DT50 values obtained for the total system for both test systems (A and B) are therefore ≤ 14.3 days, and the substance is degraded in the environment (DT50 ≤ 32 d).

[5] Sediment A: high organic matter; sediment B: low organic matter.

Only a minor part of Mifepristone was subjected to mineralisation to CO_2 and the formation of volatile compounds is negligible.

Abiotic degradation

Hydrolysis: No data on hydrolysis
Photolysis: No data on photolysis.

Justification of chosen degradation phrase:

The DT50 values for the total system are below 32 days for both test system, A and B. The phrase “Mifepristone is degraded in the environment” is thus chosen.

Bioaccumulation

Partitioning coefficient (OECD 123):

Log K_{ow} of Mifepristone was determined to be 4.61 using the slow stirring method at 25 °C (Ref. 8). This OECD protocol was chosen because an in silico estimated Log K_{ow} higher than 4 is indicated in literature. The result triggered the evaluation of the bioaccumulation potential of Mifepristone under the protocol OECD 305.

Bioaccumulation in fish (OECD 305)

Bioaccumulation of Mifepristone in zebrafish (*Danio rerio*) was evaluated using the aqueous exposure bioconcentration fish test (Ref. 9). The purpose of this study was to determine the uptake, bioconcentration and elimination of Mifepristone.

Uptake and depuration rate constants and bioconcentration factors (BCFs) for zebrafish (*Danio rerio*) exposed to Mifepristone by aqueous exposure were calculated at a single concentration. The test consists of two phases: the exposure (uptake, for a period of 26 days) and postexposure (depuration, for a period of 30 days) phases. During the uptake phase, one group of fish was exposed to the test item in treated water under continuous renewal (flow-through) conditions at a nominal concentration of 1 µg/L. The selected concentration of Mifepristone was based on the low limit of quantification of the analytical method and is far above the estimated $PEC_{SURFACEWATER}$ and therefore sufficiently high to guarantee any putative bioaccumulation effect. ^{14}C-Mifepristone was used in the study as per OECD guideline 305 recommendations.

The mean lipid content of the fish was 3.9% (start uptake phase), 5.1% (end uptake phase) and 4.5% (end depuration phase). The overall mean value (4.6%) was used for lipid normalisation. No effect on body length or weight of the fish were observed.

The overall mean concentration of Mifepristone in test water during the uptake phase was 0.90 µg/L (time weighted average), representing 90% of the target value (1 µg/L). During the uptake phase the test item concentration was considered constant. Six hours after start of the depuration phase, the test item concentration in the test water was below the limit of detection.

Steady state calculations were based on the mean tissue concentrations from days 20 to 26 of the update phase and the mean measured concentrations in whole body fish tissues during the uptake phase (steady state) was 22 µg/kg.

The bioconcentration factor was determined for steady state (BCF_{SS}), including a normalisation to 5% lipid content (BCF_{SSL}). The kinetic bioconcentration factor (BCF_{K}) was determined following estimation of the uptake rate (k1) and depuration rate (k2) constants. The BCF_{K} was corrected for growth (BCF_{Kg}) via subtraction of the growth rate constant (kg) from the k2 and normalised to 5% lipid content (BCF_{KLg}). The half-life ($t_{1/2}$) and growth corrected half-life ($t_{1/2g}$) were also determined.

Derived BCF values from the Mifepristone bioaccumulation study in fish under OECD 305 are listed below:

Steady state

BCF	BCF_{SS}	[L/kg]	23.3
Lipid normalised BCF	BCF_{SSL}	[L/kg]	25.1

Kinetic evaluation

BCF	BCF_{K}	[L/kg]	22.7
Growth-corrected BCF	BCF_{Kg}	[L/kg]	22.9
Lipid-normalised BCF	BCF_{KL}	[L/kg]	24.4

Lipid-normalised, growth-corrected BCF	BCF_{KgL}	[L/kg]	24.8
Growth-corrected half-life	$T_{1/2g}$	[d]	1.8

All bioconcentration factors estimated were below 25 L/kg and no further evaluation is required.

Adsorption coefficient in soil (OECD 106):

Adsorption/desorption behaviour of Mifepristone in different soils was evaluated. Calculated K_{oc} values were in the range 917.03 - 3390.98 and Kd_{soil} 8.2 - 12.2% (Ref. 10)

Justification of chosen bioaccumulation phrase:

Experimental Log K_{ow} is 4.61, however the estimated bioconcentration factors derived from the Mifepristone bioaccumulation study in fish as per OECD 305 were below 25 L/kg. Mifepristone bioaccumulation potential can therefore be considered to be low (BCF < 500) and the phrase “Mifepristone has low potential for bioaccumulation” is thus chosen.

Excretion (metabolism)

Mifepristone undergoes N-demethylation and terminal hydroxylation of the 17-propynyl chain to the main metabolites N-monodemethylated metabolite, N-didemethylated mifepristone and terminal hydroxylation of the mifepristone 17-propynyl chain. It is not known whether they contribute to the pharmacological

effects of Mifepristone. The major route of excretion of Mifepristone and metabolites is via the faeces (83 %) with 9 % being excreted in the urine. (Ref. 11). Due to uncertainty about the amounts metabolites excreted, worst case (i.e. 100% is excreted as the active parent molecule) is used in the PEC calculation.

PBT/vPvB assessment

Mifepristone does not meet all three properties that are required in order to classify a compound as PBT and is considered not to fulfil the criteria for PBT or vPvB.

Persistence

Mifepristone is not readily biodegradable (aerobic biodegradation study, OECD 301F) (Ref. 6). According to results obtained from the OECD 308 study (Ref. 7), DT50 values obtained for the total system for both test systems are ≤ 14.3 days. Mifepristone is thus degraded in the environment as its degradation half-life is not higher than 32 days and is not classified as a persistent compound.

Bioaccumulation

Experimental Log K_{ow} is 4.61, however bioaccumulation potential of Mifepristone is low as per OECD 305. Derived bioconcentration factors (BCF) are below 25 L/kg in all cases (Ref. 9).

Toxicity

Mifepristone is toxic for reproduction category 1 (Ref. 12) according to Regulation EC No 1272/2008 and is a known endocrine disruptor compound (EDC). As higher concentrations than 100 ng/L (NOEC) were not tested in the full life cycle study in fish it should also be considered as toxic for aquatic organism following a very conservative approach.

Mifepristone should be considered as toxic according to the PBT criteria.

References

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