FASS

Yaz

MRx EF

Bayer

Filmdragerad tablett 0,02 mg/3 mg

(De aktiva tabletterna är ljusrosa, runda med konvex yta. Ena sidan är märkt med bokstäverna ”DS” inom en liksidig sexhörning.Placebotabletterna är vita, runda med konvex yta. Ena sidan är märkt med bokstäverna ”DP” inom en liksidig sexhörning.)

Gestagener och östrogener - kombinationspreparat

Aktiva substanser (i bokstavsordning):

Drospirenon

Etinylestradiol

ATC-kod:

G03AA12

Läkemedel från Bayer omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Drospirenon

Miljörisk: Användning av drospirenon har bedömts medföra låg risk för miljöpåverkan.
Nedbrytning: Drospirenon är potentiellt persistent.
Bioackumulering: Drospirenon 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) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A*(100-R) = 0.014$ µg/L

Where:

A = 105 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):*

E_rC_{50} 72 hours (growth rate) > 7600 µg/L. Guideline OECD 201. (Reference II)

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

Acute toxicity

EC_{50} 48 hours (immobilization) > 8000 µg/L. Guideline OECD 202. (Reference III)

Chronic toxicity

NOEC 21 days (reproduction) = 556 µg/L. Guideline OECD 211. (Reference IV)

Fish (zebrafish, *Danio rerio):*

Acute toxicity

LC_{50} 96 hours (survival) = 7000 µg/L. Guideline OECD 203. (Reference V)

Chronic toxicity

NOEC 216 days (fecundity, sex ratio, histopathological changes of gonads) = 0.23 µg/L. non-standard test method – fish full life-cycle test. (Reference VI)

Microorganisms (activated sludge):

EC_{50} 30 min (respiration inhibition) > 100 mg/L. Guideline OECD 209. (Reference VII)

The PNEC was calculated by division of the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group were fish and the lowest effect level was reported as NOEC = 0.23 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 = 0.23 µg/L / 10 = 0.023 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.014 µg/L / 0.023 µg/L = 0.63.

Justification of chosen environmental risk phrase:

A risk quotient between 0.1 and 1 qualifies for the phrase “Use of Drospirenone has been considered to result in low environmental risk.”.

Degradation

Biotic degradation

Ready degradability:

Drospirenone was studied for aerobic biodegradability in water in a manometric respiration test with municipal sewage sludge. The study reported less than 3 % biodegradation of Drospirenone in 28 days. Guideline OECD 301. (Reference VIII)

Simulation studies:

The transformation of [^{14}C] drospirenone in sediments and natural water was assessed in two different aerobic and anaerobic sediment/water systems at a temperature of 20 ± 2 °C continuously in the dark according to guideline OECD 308. Water and sediment were extracted for radio-HPLC separation, by using various extraction solvents such as acetonitrile, acetonitrile/water mixture and acetonitrile/HCl mixture. For mass balance determination, aquatic samples were measured by liquid scintillation counting, sediment samples combusted.

Only slight ultimate biodegradation was observed in the test systems. The accumulative amount of evolved $^{[14]}CO_2$ for the aerobic test systems was 1.4 and 3.8 % of the applied radioactivity.

Primary degradation was observed for drospirenone to a low degree in the water/sediment test samples. Two fractions with degradation products were observed in the HPLC analysis. Since the main metabolite appeared from day 3 onwards (although not continuously in the water phase), it is likely, that this metabolite is the isomer ZK 35096 (10). Because the second metabolite occurred only at day 37 (one replicate) and day 59 in one sediment type, it is of minor importance.
Dissipation was determined with DT_{50}, DT_{75} and DT_{90}values in the water layer of the aerobic transformation with 2.1, 4.1and 6.8 days for high organic carbon sediment system and 2.2, 4.5 and 7.5 days for low organic carbon system. The degradation DT_{50}, DT_{75} and DT_{90} values in the total system were 9.9, 20 and 33 days for high organic carbon sediment system and 36, 72 and 119 days for low organic carbon system. The calculated systems half-lives, however, are very hypothetical, since there was no clear trend of decreasing concentrations of the extracted [14C] drospirenone between day 0 and day 100.
Therefore, the half-life of drospirenone in the environment is considered to exceed the threshold of 120 days. Guideline OECD 308. (Reference IX)

Abiotic degradation

Hydrolysis:
This study reported a half-life of > 12.8 days to a non-active isomer at pH 7. Guideline EC C7 (HPLC method). (Reference X)
Justification of chosen degradation phrase:
Drospirenone established a DT_{50} > 120 d for the total system which qualifies for the phrase “Drospirenone is potentially persistent.”.

Bioaccumulation

Partitioning coefficient:
The log D_{ow} was reported with 3.1 at pH 7. Guideline OECD 117. (Reference XI)
Bioconcentration factor (BCF):
The study with drospirenone was conducted in the bluegill sunfish Lepomis macrochirus. Concentrations were 0.1 and 1.0 µg/L [14C]drospirenone. The fish were exposed over 35 days with a subsequent depuration phase of 29 days.
The steady state bioconcentration factors for total radioactive residue were 97 and 99 for the 0.1 and 1.0 µg/L treatment level, respectively, based on lipid content of 4.83 %. Normalised to 5% fat tissue, the BCFss for whole fish are 100 and 102 for the 0.1 and 1.0 µg/L treatment levels, respectively. Guideline OECD 305. (Reference XII)
Justification of chosen bioaccumulation phrase:
As the log D_{ow} was < 4 and/or BCF < 500 Drospirenone is not considered bioaccumulative which qualifies for the phrase “Drospirenone has low potential for bioaccumulation.”.

Excretion (metabolism)

Drospirenone is only to a small extent excreted unchanged. Conjugates such as glucuronides and sulphates as well as hydroxylated compounds were identified. (Reference XIII, XIV)

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 drospirenone on the green algae Scenedesmus subspicatus. Experimental Toxicology, Schering AG, study no. TX1997085, report no. AU49 (1997)

III. Acute immobilization of drospirenone with Daphnia magna. Experimental Toxicology, Schering AG, study no. TX97141, report no. AT51 (1997)
IV. Reproduction study of drospirenone (ZK 30595) in Daphnia magna. Nonclinical Drug Safety, Bayer HealthCare AG, study no. TOXT6082178, report no. A52014 (2011)
V. Acute toxicity of drospirenone to the zebrafish (Danio rerio). Experimental Toxicology, Schering AG, study no TX97042, report no. AU44 (1997)
VI. Full-life-cycle-tests with drospirenone (BAY 86-4888) on the fathead minnow (Pimephales promelas). Nonclinical Drug Safety, Bayer HealthCare AG, study no TOXT6082898, report no. A62532 (2011)
VII. Respiration inhibition gest of drospirenone (ZK 30595) on activated sludge micro organisms. Nonclinical Drug Safety, Bayer Schering Pharma AG, study no TXST20070211, report no. A40777 (2008)
VIII. Study on the biodegradability of drospirenone in the CO2- evolution test (modified Sturm-test). Experimental Toxicology, Schering AG, study no. TX97155, report no. AT51 (1997)
IX. [14C] Drospirenone: Aerobic and anaerobic transformation in aquatic sediment systems). Nonclinical Drug Safety, Bayer Schering Pharma AG, study no. TXEX20070018, report no. A48365 (2008)
X. The rate of hydrolysis of drospirenone (ZK 30595). General Physical Chemistry, Schering AG, study no. 1274, report no. LY67 (1997)
XI. The determination of the n-octanol-water partition coefficient of ZK 30595. General Physical Chemistry, Schering AG, study no. 1290, report no. LY66 (1997)
XII. [14C] Drospirenone: Bioconcentration study with bluegill sunfish (Lepomis macrochirus) under flow-through conditions. Nonclinical Drug Safety, Bayer Schering Pharma AG. Study no. TXEX20070017, report no. A48324
XIII. Absolute and relative bioavailability of ZK 30595 after oral administration of SH T 470 C and SH T 470 D, respectively to 8 young women. Schering AG, Pharmacokinetics/Biometrics/Human Pharmacology, study no. KI87053, report no. 8235 (1990)
XIV. Absolute bioavailability, excretory balance, and qualitative investigation of the biotransformation of 14C-ZK 30595 following i.v. and p.o. administration in healthy, elderly female volunteers. Schering AG, Pharmacokinetics, study no. KI93037, report no. A166 (1995)

Etinylestradiol

Miljörisk: Användning av etinylestradiol har bedömts medföra hög risk för miljöpåverkan.
Nedbrytning: Etinylestradiol bryts ned i miljön.
Bioackumulering: Etinylestradiol har hög potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A*(100-R)$ = 0.00037 µg/L

Where:

A = 2.691 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) = 117 µg/L, E_rC_{50} 72 hours (growth rate) = 460 µg/L. Guideline OECD 201. (Reference II)
*Crustacean (*waterflea, *Daphnia magna):*
Acute toxicity
EC_{50} 48 hours (immobilization) = 6400 µg/L. Guideline OECD 202. (Reference III)
Chronic toxicity
NOEC 21 days (reproduction) ≥ 387 µg/L. Guideline FDA TAD 4.09. (Reference IV)
Fish:
Acute toxicity *(*rainbow trout, *Oncorhynchus mykiss)*
LC_{50} 96 hours (survival) = 1600 µg/L. Guideline FDA TAD 4.11. (Reference V)
Chronic toxicity *(*fathead minnow, *Pimephales promelas)*
NOEC 300 days (life-cycle test: growth, sexual development) = 0.001 µg/L. Guideline OECD EPA FIFRA Subdev. E, 72-5. (Reference VI)

The PNEC was calculated by division of the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group was fish, and the lowest effect level was reported as NOEC = 0.0003 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 = 0.0003 µg/L / 10 = 0.00003 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.00037 µg/L / 0.00003 µg/L = 12.3.
Justification of chosen environmental risk phrase:
A risk quotient above 10 qualifies for the phrase “Use of ethinylestradiol has been considered to result in high environmental risk.”.

Degradation

Biotic degradation

Ready degradability:
Ethinylestradiol was studied for aerobic biodegradability in water in a CO_2 evolution test according to guideline FDA TAD 3.11 (8). Ethinylestradiol was introduced into the test system at a concentration of 10 mg/L as carbon. The study reported 3 % biodegradation of ethinylestradiol in 28 days, wherefore the substance is considered not readily biodegradable. Guideline FDA TAD 3.11. (Reference VII)
Simulation studies:
A study on transformation in aquatic/sediment systems according to test guideline OECD 308 was conducted. The transformation of [14C] ethinylestradiol in sediments and natural water was assessed in three different aerobic sediment/water systems. The disappearance half-lifes of [14C] ethinylestradiol were in the overlying water of aerobic systems 4.0 and 5.9 days for the high and low organic carbon content, respectively. Since for one of the low organic carbon content sediment the total mass balance was not reached as recommended in the guideline OECD 308 (≥ 90%), this result was not further evaluated.
The extraction from sediments were performed by the following method, which was validated for spiked sediments prior to application to test samples: The sediment is extracted by using 50 mL acetonitrile:water, 80:20, v:v as extraction solvent. If more than 5 % of the applied amount is found in the second extract the sediment is extracted a third time using acetonitrile:1 M HCl 80:20, v:v. A portion of the combined extracts was then reduced by rotary evaporation at 40 °C and at least 60 mbar. The concentrated sample was then analyzed by HPLC for parent compound and extractable metabolites.

The parent compound was recovered to 0 % from all water and sediment samples at day 99. Only slight ultimate biodegradation was observed in the test systems. The accumulative amount of evolved $^{14}CO_2$ for the aerobic test systems was 2.5 and 5.1 % of the applied radioactivity. Primary degradation was observed for ethinylestradiol to a low degree in the water/sediment test samples. One metabolite occurred only occasionally. Most of the introduced radioactivity was sediment-bound (50-62 %).
In the total water/sediment systems the DT_{50} of [14C] ethinylestradiol was 24, 36, and 28 days for the 2 systems. The DT_{50} values differed ranked in two cases below the threshold of 32 days and exceeded this threshold in one case. Since two of three water-sediment systems report DT_{50} below the criterion and the exceedance of one system is moderate, ethinylestradiol can be classified as being degradable.
In conclusion, this study reported a half-life of ethinylestradiol of 4.0-5.9 days in water and 24-36 days in sediment/total system. Guideline OECD 308. (Reference VIII)

Abiotic degradation

Hydrolysis:
This study reported that ethinylestradiol is hydrolytically stable. Guideline FDA TAD 3.09. (Reference IX)
Justification of chosen degradation phrase:
The degradation half-life in the total system of the OECD 308 study qualifies for the phrase “ethinylestradiol is degraded in the environment”.

Bioaccumulation

Partitioning coefficient:
The log D_{ow} was reported as 4.2. Guideline FDA TAD 3.02. (Reference X)
Bioconcentration factor (BCF):
A bioaccumulation study with ethinylestradiol was conducted in the bluegill sunfish *Lepomis macrochirus*. The fish were exposed to concentrations of 1 and 10 ng/L [14C] ethinylestradiol, over 35 days with a subsequent depuration phase of 29 days. The steady state bioconcentration factors (BCFs) for total radioactive residue were 371 and 634 for the 1.0 and 10 ng/L treatment level, respectively. The steady state bioconcentration factors for total radioactive residue (TRR) based on lipid content of 3.61 % were 371 at the 1.0 ng/L treatment level and 634 at the 10 ng/L treatment level. Normalised to 5 % fat tissue, the BCFss for total radioactive residues for whole fish are 514 and 878 for the 1.0 and 10 ng/L treatment levels, respectively. Guideline OECD 305. (Reference XI)
Justification of chosen bioaccumulation phrase:
As the log D_{ow} was > 4 and BCF > 500 ethinylestradiol is considered bioaccumulative which qualifies for the phrase “ethinylestradiol has high 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 ethinylestradiol (ZK 4944) on the green algae *Desmodesmus subspicatus*. Experimental Toxicology, Schering AG, Study no. TXST20020060, Report no. A12518 (2004).
III. Acute immobilization of ethinylestradiol with *Daphnia magna*. Experimental Toxicology, Schering AG, Study no. TXS94269, Report no. AG47 (1997).
IV. Chronic toxicity study of ethinylestradiol on *Daphnia magna*. Experimental Toxicology, Schering AG, Study no. TXS94268, Report no. AG95 (1999).
V. Acute toxicity test of ethinylestradiol with rainbow trout. Experimental Toxicology, Schering AG, Study no. TX93145, Report no. A987 (1995).

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VII. Study on aerobic biodegradation of ethinylestradiol. Experimental Toxicology, Schering AG, Study no. TX93157, Report no. AA74 (1995).
VIII. [14C] Ethinylestradiol: Aerobic and anaerobic transformation in aquatic sediment systems. Bayer Schering Pharma AG, Nonclinical drug Safety, Springborn Smithers Laboratories, Horn, Switzerland study no. 1121.000.753 (2008).
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X. [14C] Ethinylestradiol: Bioconcentration study with bluegill sunfish (*Lepomis macrochirus*) under flow-through conditions. Bayer Schering Pharma AG, Nonclinical drug Safety, Springborn Smithers Laboratories, Horn, Switzerland study no. 1121.000.135 (2008).