FASS

Faslodex®

AstraZeneca

Injektionsvätska, lösning i förfylld spruta 250 mg
(Tillhandahålls ej) (klar, färglös till gul, viskös lösning)

Medel mot tumörer, endokrint verksamt, antiöstrogen

Aktiv substans:
Fulvestrant

ATC-kod:
L02BA03

Läkemedel från AstraZeneca omfattas av Läkemedelsförsäkringen.
Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Fulvestrant

Miljörisk: Användning av fulvestrant har bedömts medföra låg risk för miljöpåverkan.
Nedbrytning: Fulvestrant bryts ned i miljön.
Bioackumulering: Fulvestrant har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 0.00033 µg/L /0.00057 µg/L = 0.60
PEC/PNEC ≤ 1

Environmental Risk Classification

Predicted Environmental Concentration (PEC)
The PEC is based on following data:

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

PEC =1.37 * 10^{-6} * 4.89* (100 – 50)

= 0.00033 µg/L

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

= 4.89 kg

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)

= 50 (conservative estimate based on OECD303a, Ref. 15)

P = number of inhabitants in Sweden = 10*10^{6}

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

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

(Note: The factor 10^{9} converts the quantity used from kg to µg).

Metabolism

The metabolism and excretion of fulvestrant in man has been determined following intramuscular and intravenous administration. Fulvestrant is rapidly metabolised via a number of biotransformation pathways, analogous to those of endogenous steroids (oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate and oxidation of the side chain sulphoxide). The metabolism profile in humans similar to that found in other mammalian species. Identified metabolites are either less active or exhibit similar activity to fulvestrant. The major route of excretion is via the faeces (~80-90%) with less than 1% being excreted in the urine (Ref 2, 3 and 4). In humans the metabolite profiles observed in faeces comprised of 10 to 15 components. The two largest fractions of these profiles were unchanged fulvestrant and the sulphone metabolite which represented approximately 8-6% of the administered dose.

Ekotoxicity data

Endpoint	Species	Common Name	Method	Time	Result	Ref.
EC50 – Based on Growth Rate	*Selenastrum capricornutum*	Green Alga	OECD 201	72 h	> Limit of Solubility *Note 1*	5
NOEC					Limit of Solubility	
EC50 – Based on Immobilisation	*Daphnia magna*	Giant Water Flea	OECD 202	48 h	> Limit of solubility *Note 2*	6
NOEC					Limit of solubility	
LOEC- Based on Reproduction & Length	*Daphnia magna*	Giant Water Flea	OECD 211	21 d	≥ Limit of solubility *Note 3*	7
NOEC					Limit of solubility	
LC50 – Based on Mortality					> Limit of solubility *Note 4*	

Endpoint	Species	Common Name	Method	Time	Result	Ref.
NOEC	*Oncorhynchus mykiss*	Rainbow Trout	OECD 203	96 h	Limit of solubility	8
LOEC – Based on F_1 length and dry weight	*Pimephales promelas*	Fathead Minnow	EPA 540/9-86-137 1986 Pair breeding study with em bryo-larval test	43 d	22.2ng/L *Note 5*	9
NOEC					5.7ng/L *Note 5*	
LOEC – Based on F_0 fecundity					0.143ng/L	
NOEC					>0.143ng/L	
LOEC - Based on emergence & development rate	*Chironomus riparius*	Midge	OECD 218	28 d	>5 mg/kg (dry weight) *Note 6*	10
NOEC					5 mg/kg (dry weight)	
ASRIT - Activated Sludge Respiration Inhibition	-	-	OECD 209	3 h	>100 mg/L *Note 7*	11
NOEC					100 mg/L *Note 7*	

Note 1: Limit of solubility below limit of detection 0.047 mg/L

Note 2: Limit of solubility below limit of detection 0.051 mg/L

Note 3: Limit of solubility below limit of detection 0.030 µg/L

Note 4: Limit of solubility below limit of detection 0.028 mg/L

Note 5: Results are expressed as mean measured concentrations.

Note 6: Concentrations confirmed with radiochemical analysis

Note 7: Results are expressed as nominal concentrations.

PNEC (Predicted No Effect Concentration)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on results from the assessment of the fathead minnow (*Pimephales promelas*) study;
NOEC = 5.7ng/L = 0.0057µg/L and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref 12).

PNEC = 0.0057/10 µg/L = 0.00057 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.00033 µg/L /0.00057 µg/L = 0.60; i.e., PEC/PNEC >1

In Swedish: ”Användning av fulvestrant har bedömts medföra låg risk för miljöpåverkan” under the heading ”Miljörisk”.

Environmental Fate Data

Endpoint	Method	Concentration	Time	Result	Ref.
BOD	OECD 301F	100 mg/l	5 d & 28 d	< 0.05 g O_2/g	13
Percentage Aerobic Biodegradation			28 d	< 5 %	
Percentage Inherent Biodegradation	OECD 302A DoE (1981) Method H	0.003 mg/l	41 d	< 0.9 % Mineralisation	14
Percentage Compound Removal (STP Simulation)	OECD 303A	0.001 mg/l (Nominal)	93 d (29 d equilibrium, 64 d exposure)	100 %	15
Biodegradation Half-life (STP Simulation)				T1/2 = 21.7 h Mineralisation	
Degradation Half-Life	OECD 308	0.1 mg/l (Nominal) (High Organic Matter Sediment)	99 d	DT50 = <14 days (Total System)	16
		0.1 mg/l (Nominal) (Low Organic Matter Sediment)		DT50 = <14 days (Total System)	
Percentage Compound Removal		0.1 mg/l (Nominal) (High Organic Matter Sediment)		>75	
		0.1 mg/l (Nominal) (Low Organic Matter Sediment)			

Biodegradation

Fulvestrant is not readily biodegradable according to OECD 301F (Ref 13) and not inherently biodegradable according to OECD 302A (Ref 14).

However, in a sewage simulation test, OECD 303A (Ref 15), total radioactivity was shown to partition evenly between the aqueous effluent and sludge solids. Unchanged [^{14}C]fulvestrant was not identified in the aqueous effluent extracts and degradation products did not exceed 10% of the applied radioactivity (AR) and no attempt was made to identify them. Samples of the activated sludge at the end of the exposure period were extracted using methanol, which attained 84% recovery of the bound radioactivity, and the

radioactivity was characterised in a separate study (Ref 17). This analysis also confirmed that the remaining radioactivity bound to the activated sludge was present as degradation products. Again, no individual degradation product exceeded 10% of AR and no attempt was made to identify them.

Overall, the results from these studies show that fulvestrant is likely to be significantly degraded following sewage treatment and a conservative assumption of 50% removal by sewage treatment is factored into the PEC calculation above.

The evidence from the OECD 308 study (Ref 16) shows that fulvestrant entering the aquatic environment is likely to rapidly dissipate from the water phase into the sediment and undergo significant degradation.

Non-extractable residues (NER) increased throughout the study. At Day 99, 44% and 56% of the AR in the HOM and LOM, respectively, was associated with the NER. At Day 49 a variety of extraction solvents (methanol, methanol:dichloromethane (DCM) 50:50, acetone, acetonitrile, tetrahydrofurane (THF), hexane, DCM, chloroform, ethyl acetate and toluene) were used to minimise the amount of NER, however no significant increase in recovery was observed.

By Day 14 (the first data point after Day 0) approximately 13% and 9.5% of the AR remained in the aqueous phase, of which <10% was present as fulvestrant. At Day 14, approximately 82% and 65% of the AR was extracted from the high (HOM) and low (LOM) organic carbon sediments, respectively, using Soxhlet extraction. Specific analysis of the HOM sediment extract showed that fulvestrant accounted for approximately 13% of the AR. No fulvestrant was observed in the extract of the LOM sediment.

The presence of fulvestrant in the HOM sediment extract declined throughout the study, at Day 99 fulvestrant accounted for <2% of the radioactivity extracted from the sediment phase.

In the HOM sediment extract two degradation products were observed that accounted for >10% AR. No degradation products accounting for >10% AR were observed in the LOM sediment extract.

At the end of the test mineralisation (formation of $^{14}CO2$) accounted for 6% in the HOM and 13% in the LOM, a further 3% AR was associated with the volatile organic degradation products.

Evidence from this study suggests that in the aquatic environment fulvestrant will partition to the sediment and be degraded.

- Radio-TLC analysis of the extracts from the high organic matter systems showed no fulvestrant parent in the water phase after day zero.
- Fulvestrant residues in the sediment extracts peaked on day 14 (13% AR) and declined to 1.7% AR at the end of the study.

Although insufficient time points were available for robust kinetic half-life determination, fulvestrant accounted for <25% of the AR by Day 14, resulting in an estimated total system half-life <14 days for fulvestrant.

Based on the evidence of the OECD303A and 308 the phrase “Fulvestrant is degraded in the environment” is assigned.

In Swedish: “Fulvestrant bryts ned i miljön” under the heading “Nedbrytning”.

Physical Chemistry Data

Endpoint	Method	Test Substance Conditions	Result	Ref.
Partition Coefficient Octanol Water	OECD 123	-	Log P = 7.67	18
Water Solubility	OECD 105	20^{o}C @ pH7	0.00078 - 0.0032 mg/L	19

Bioaccumulation

Endpoint	Species	Common Name	Method	Test Substance Conc.	Result	Ref.
Bio-concentration factor (Whole Body -Based on Total Measured Radioactivity)	*Oncorhynchus mykiss*	Rainbow trout	OECD 305	0.0001 mg/l (Nominal)	BCF steady state = 342 Kinetic BCF = 355	20
				0.001 mg/l (Nominal)	BCF steady state = 338 Kinetic BCF = 357	

Although fulvestrant has a high octanol-water coefficient, the bioconcentration factors determind in the OECD305 Bioaccumulation in fish study indicated that the risk of bioaccumulation of fulvestrant in aquatic organisms is low. Therefore, the phrase “Fulvestrant has low potential for bioaccumulation” is assigned.

In Swedish: ”Fulvestrant har låg potential att bioackumuleras.” under the heading “Bioackumulering”.

References

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