FASS

Inderal®

M ℞ (F)

AstraZeneca

Filmdragerad tablett 10 mg
(rosa-färgad, skåra, 6,5 mm)

ß-receptorblockerare

Aktiv substans:
Propranolol

ATC-kod:
C07AA05

Läkemedel från AstraZeneca omfattas av Läkemedelsförsäkringen
.

Miljöpåverkan

Propranolol

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

Detaljerad miljöinformation

PEC/PNEC = 0.018 µg/L /0.23 µg/L = 0.078 → PEC/PNEC ≤ 0.1

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is based on following data:

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

PEC (µg/L) = $1.5*10^{-6}*A*(100-R)$

A (kg/year) = total actual API sales (active moiety) in Sweden 2014.
R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization,
hydrolysis or biodegradation).
P = number of inhabitants in Sweden = $9 *10^{6}$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default)
D = factor for dilution of waste water by surface water flow = 10 (ECHA default)
(Note: The factor 10^{9} converts the quantity used from kg to µg).

A = 902.920 kg. This figure is based on sales figures from IMS for 2014 for propranolol hydrochloride.

R = 87%. The removal during sewage treatment (86.5%) is estimated using the EUSES model (which contains Simple Treat) described in the ECHA Technical Guidance Document (Ref 1) where

following assumptions have been made: propranolol is readily biodegradable, with vapor pressure (VP) $<5*10^{-6}$ Pa, water solubility 97.9 g/L (Ref 26) and Kd_{sludge} = 480 L/kg (Ref 28). Propranolol is an involatile solid with negligible VP at ambient conditions, a measured VP is not available and therefore the nominal value used in this calculation assumes no losses to the atmosphere.

$PEC = 1.5 * 10^{-6} * 902.920 * (100 - 87) = 0.018 \mu g/L$

Metabolism and excretion

Propranolol hydrochloride is extensively metabolized in the body, and excreted mainly via the urine, less than 5% of the given dose via faeces (Ref 2). Only a little part is excreted as the parent compound however, approximately 17% of the given dose is excreted as a conjugated propranolol which could potentially de-conjugate to parent propranolol during sewage treatment (Ref 3).

Ecotoxicity Data

Propranolol Hydrochloride

Endpoint	Species	Common name	Time	Result (mg/L)	Method	Reference
NOEC Growth	*Synechococcus leopoliensis*	Cyano-bacterium	96 h	0.35	Growth inhibition test	4
		Diatom	96 h	0.094		4

Endpoint	Species	Common name	Time	Result (mg/L)	Method	Reference
NOEC Growth	*Cyclotella meneghiniana*				Growth inhibition test	
EC10 Growth rate	*Phaeodactylum tricornutum*	Diatom	72 h	0.09	Growth inhibition test	5
NOEC Growth	*Pseudokirchneriella subcapitata*	Green algae	96 h	5.0	Growth inhibition test	4
NOEC Growth				0.11		6
NOEC Biomass			72 h	<0.78	OECD 201 (microplate fluorescence method)	7
NOEC Growth	*Lemna minor*	Common duckweed	7 d	>100	DIN AK 2000	8
NOEC Reproduction	*Brachionus calyciflorus*	Rotifer	48 h	1	ISO/DIN 20666	7
				0.18	AFNOR T90-377	4
			9 d	0.055		9

Endpoint	Species	Common name	Time	Result (mg/L)	Method	Reference
NOEC Fecundity	*Daphnia magna*	Giant water flea			Modified USEPA 1994	
NOEC Growth				0.22		
NOEC Fecundity			21 d	<0.05	Adapted OECD 211	10
NOEC Immobilisation				0.20		
NOEC Fecundity	*Ceriodaphnia dubia*	Water flea	7 d	0.009	US EPA Method 1002.0	4
NOEC Egg production and Hatchability	*Pimephales promelas*	Fathead minnow	21 d	0.11	Non-standard adult reproduction	11
NOEC Growth	*Oncorhynchus mykiss*	Rainbow trout	10 d	1.0	OECD 215	12
NOEC Growth	*Danio rerio*	Zebra FIsh	10 d	2	ISO 12890	4
NOEC Hatching rate			96h	4	Based on OECD 236	13

Endpoint	Species	Common name	Time	Result (mg/L)	Method	Reference
NOEC Growth	*Pimephales promelas*	Fathead minnow	7 d	<0.128	US EPA Method 1000.0	9

Propranolol Base

Endpoint	Species	Common name	Time	Result (mg/L)	Method	Reference
NOEC Reproduction	*Ceriodaphnia dubia*	Water flea	7 d	0.125	US EPA 1991	14
NOEC Larval Length	*Paracentrotus lividus*	Sea urchin	48 h	0.005	Non standard Embryogenisis [note 1]	15
NOEC Larval Abnormality				0.002		
NOEC Mortality & Hatching rate	*Danio rerio*	Zebra fish	80 hpf[a]	1.25	OECD 212	15

[a] hpf = hours post fertilization

Note 1: further detail of the study design and endpoints are given in Appendix 1

Predicted No Effect Concentration (PNEC)

Reliable long-term ecotoxicity data for propranolol hydrochloride is available for representatives from three trophic levels (algae, invertebrates and fish) and for propranolol base for representatives from two trophic levels (invertebrates and fish). The lowest NOEC is 0.002 mg/L, since the effect concentration was derived for propranolol base (molecular weight 259.343 g/mol) and the assessment is for the hydrochloride salt (molecular weight 295.808 g/mol) the NOEC is adjusted, by a factor of 1.14, based on the molecular weight and an assessment factor of 10 is applied to derive the PNEC, in accordance with the guidance.

PNEC = (2.0 µg/L x 1.14) /10 = 0.23 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.018 µg/L /0.23 µg/L = 0.078
PEC/PNEC ≤ 0.1

The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase, and the risk phrase for PEC/PNEC ≤ 0.1 reads as follows:
“Use of propranolol has been considered to result in insignificant environmental risk”
In Swedish: ”Användning av propranolol har bedömts medföra försumbar risk för miljöpåverkan” under the heading ”Miljörisk”.

Environmental Fate Data

Propranolol Base

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
Biodegradation	Based on OECD 301B @ sludge conc. 30 mg/L	0.01 and 0.1 mg L^{-1}	10d	> 60% Readily biodegradable	16
	Based on OECD 301B @ sludge conc. 3000 mg/L	0.01 and 0.1, 100 mg L^{-1}			
Percentage Mineralisation	Modified OECD 301B & OECD 302B	low sludge; 0.1, 1, 10 & 100 mg/L	80d	15.9 - 30.9%	17
		high sludge; 0.1, 1, 10 mg/L		20.5 - 30.8%	
		high sludge; 100 mg/L		70.6%	
		100 µg/L	28 d		18

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
Biodegradation Half life	OECD 301A – DOC die-away			DT50: 120 h DT50: 620 h	
Biodegradation	OECD 301A and OECD 310	0.1 and 1.0 mg/L	28d	≥60% biodegradation	19
Transformation Half life	OECD 309 study, degradation in freshwater	1.0 and 0.1 mg/L in two River Waters	60d	Water at 20°C DT50: 52.1 d DT50: 54.6 d DT50: 16.2 d DT50: 24.2 d	20
	similar to OECD 308	5 µg/vessel at 22°C Burgen sediment (TOC 0.74%, clay/silt 10%)		Total system DT50: 33 d DT50: 9.9 d	21

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
		Dausenau Sediment (TOC 4.36%, clay/silt 47%)			
Bioconcentrat-ion Factor (Whole Body)	*Mytilus edulis trossulus* (Baltic Sea Blue Mussels) Method unknown	0.001 - 10 mg/L	8 d	BCF = ca 160	22
Partition Coefficient Octanol Water	OECD 107	pH 4, 20°C pH 5, 20°C pH 6, 20°C pH 7, 20°C pH 8, 20°C pH 9, 20°C		Log P = 1.6 Log P = 1.4 Log P = -0.12 Log P = 0.72 Log P = 1.6 Log P = 2.6	23
					24

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
	pH Metric Method	Neutral form		Log P = 3.48	

Propranolol Hydrochloride

Endpoint	Method	Test Substance Concentration	Time	Result	Reference
Partition Coefficient Octanol Water	OECD 107	pH 5 pH 6 pH 9	-	Log P = 1.42 Log P = 0.018 Log P = 2.82	25
		pH 5 pH 7 pH 9		Log P = 1.39 Log P = 0.722 Log P = 2.63	23

Degradation

Under conditions of the OECD301B test, propranolol hydrochloride fulfilled the criteria for ready biodegradability at 0.1 mg/L, more than 60% mineralization was achieved. In the highest concentration of propranolol hydrochloride (100 mg/L) with the lowest concentration of sludge (30 mg/L), propranolol could not be

classified as readily biodegradable. However, at higher sludge concentration (3000 mg/L), comparable to those of most sewage treatment works, propranolol was found to be readily biodegradable at 100 mg/L.

Based on this information, propranolol has been assigned the risk phrase: ‘Propranolol is degraded in the environment’.

In Swedish: “Propranolol bryts ner i miljön” under the heading “Nedbrytning”.

For estimating PEC, the removal during sewage treatment (R) is estimated using the ECHA Technical Guidance Document (Ref 1) where following assumptions have been made: propranolol is readily biodegradable, with vapor pressure $<5*10^{-6}$ Pa, water solubility 97.9 g/L (Ref 26) and Kd_{sludge} = 480 L/kg (Ref 28), ending up in R = 86.5%.

Bioaccumulation

Since BCF < 500, and Log P < 4 at pH intervals 4-9, propranolol has low potential to bioaccumulate and the phrase ‘Propranolol has low potential for bioaccumulation’ is assigned.

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

Physical Chemistry Data

Propranolol Hydrochloride

Endpoint	Method	Test Conditions	Result	Reference
Solubility Water	UV Spectrophotometry	25°C	97.9 g/L	26
Dissociation Constant	Unknown	-	9.53	27
Sludge Adsorption Coefficient	OPPTS 835.110	0.1 mg/L, 20 °C	Kd = 390- 420	28
Adsorption characteristics	OECD 106	Low Organic Carbon, High Clay Soil, pH 6.8	Kd = 16.3 Koc = 4405	27
		High Organic Carbon, Low Clay Soil, pH 4.3	Kd = 199 Koc = 2803	

Propranolol Base

Endpoint	Method	Test Conditions	Result	Reference
Solubility Water	Unknown	-	609.4 mg L	4
Dissociation Constant	Unknown	-	9.53	24
Sediment Adsorption Coefficient	OECD 106	River Burgen Sediment, Clay/Silt 10 %, pH 6.6	Log Koc = 2.66	29

Endpoint	Method	Test Conditions	Result	Reference
		River Dausenau River Sediment, Clay/Silt 47%, pH 6.5	Log Koc = 2.43	
Adsorption characteristics		Akui River Sedimen, pH 6.7	Kd = 2.2 Koc = 2900	18
		Tamiya River Sediment, pH 6.6	Kd = 100 Koc = 10000	
		Tatara River Sediment, pH 5.7	Kd = 160 Koc = 9400	
		Elliot Silt Loam Soil, pH 6.6	Kd = 1100 Koc = 50000	

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Appendix 1

Experiments involving the fertilisation and development of sea urchin eggs and embryos have been accepted internationally as appropriate for toxicity tests (U.S. EPA, 1995; Environment Canada, 1997; CETESB, 1999). Direct measurement of growth and development are considered relevant for PNEC derivation. A summary of the experimental design reported in Ribero et al 2015 (Ref 15) is presented below, based on the criteria of Klimisch et al 1997, reliability category 2 is assigned.

Organisms: sea urchins were collected in Portugal (N41° 2’26, 18”, W -8° 39’2, 24”), eggs and sperm were extracted and toxicity tests were performed when fertilisation rate was >97%.

Media: Artificial seawater; Potassium chloride (0.67 g/L),Calcium chloride(1.36 g/L),Magnesium chloride hexahydrate (4.66 g/L), Magnesium sulphate (2.04 g/L), Sodium chloride (24.6 g/L) and Sodium bicarbonate (0.39 g/L).

Test Vessels: 24-well plates containing 3 ml solution (20 eggs/mL), 8 well replicates per treatment.

Test concentrations: Prepared by serial dilution, stock solutions prepared Dimethylsulfoxide (DMSO), experimental solutions obtained via dilution with artificial sea water, final DMSO concentration 0.01%.

Experimental design: Control and solvent control (grouped for statistical analysis) seven test concentrations; 0.8, 2.0, 5.0, 12.5, 125, 1250, 12500 µg/L.

48 hour exposure, at 20°C in the dark.

At the end of the exposure embryos were fixed by adding three drops of 37% formaldehyde and directly observed under an inverted microscope. Assessment criteria for development are described within the paper. End points; larval length (n = 240 for controls; n = 120 for exposed groups), Percentage total abnormalities (n = 320 for controls; n =160 for exposed groups). The number of analyzed individuals for the two criteria was based on Saco-Álvarez et al (2010).

Results: All data were tested for normality and homogeneity of variances prior to testing for significance analysis using appropriate parametric/non-parametric tests as required. Statistically significant reductions ($P < 0.05$) in larval length at ≥ 12.5 ug/L. Statistically significant increase in the percentage of abnormal organisms at ≥ 5 ug/L.
48 hour larval length NOEC = 5 µg/L
48 hour larval abnormality NOEC = 2 µg/L

Appendix 1 References:

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