FASS

Naprosyn® Entero

Pharmanovia

Enterotablett 500 mg
(vit, oval, märkt "NPR EC 500" på ena sidan)

Antiflogistikum med analgetisk och antipyretisk effekt

Aktiv substans:
Naproxen

ATC-kod:
M01AE02

Läkemedel från Pharmanovia omfattas av Läkemedelsförsäkringen
.

Miljöpåverkan

Naproxen

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

Detaljerad miljöinformation

PEC/PNEC =0.59/0.64 = 0.92 for Naproxen which means that the phrase 'Use of the medicine has been considered to result in low environmental risk.' is used for Level 1 and 2.

The PEC is based on the following data:
A = 11893.6 kg Naproxen (use data from Läkemedelsstatistik AB, LSAB, 2010)
PEC = $1.5 \times 10^{-6} \times 11893.6 \times (100–67) = 0.59$ µg/l

Ecotoxicological studies: [5]
Green alga *(Desmodesmus subspicatus)*:
ErC50 72 h =39 000 µg/l (OECD 201)
NOEC 72 h = 3 900 µg/l (OECD 201)

Water-flea *(Daphnia magna)*:
EC50 48 h = 37 000 µg/l (OECD 202)
Water-flea chronic *(Ceriodaphnia dubia)*:
chronic NOEC 192 h = 32 µg/l (Environment Canada Method)

Rainbow trout *(Oncorhynchus mykiss)*:
LC50 96 h = 52 000 µg/l (OECD 203)

Micro-organisms:
NOEC = 30 000 µg/l (toxicity control in inherent biodegradation test)

The PNEC is based on the following data:
The PNEC is based on the lower of two chronic NOECs available (water-flea, *Ceriodaphnia*) and 50 is the assessment factor used.
PNEC = 32/50 = 0.64 µg/l

Degradation:
Naproxen is not readily biodegradable, however, it is inherently biodegradable and actual, measured elimination rates in various sewage works range from 0% to >99%, with a median of approximately 67%. Moreover, naproxen in surface waters is short-lived, due to biodegradation and photolysis in superficial layers (which is *not* included in the above PEC calculation). A surface water half-life in late summer in Switzerland at ~47° N was determined at 14 days. Hence, naproxen is rapidly degraded in sewage works and surface waters and is nonpersistent. [5]

Bioaccumulation:
Naproxen has no significant bioaccumulation potential, with measured logD values below 1.1 at pH 6.5–7.4.

Excretion/metabolism:
Subsequent to oral application, naproxen shows rapid uptake, very high bioavailability (~99%) and equally high plasma protein binding. The plasma half-life is around 14 (12–15) h, longer in older people. Approximately 30% of absorbed naproxen undergoes Phase I metabolism through 6-O-demethlyation in liver microsomes, which is mediated by cytochrome P450 (CYP) enzyme isoforms CYP2C9 and CYP1A2. Both the approximately 70% native and the 30% 6-O-desmethyl naproxen subsequently undergo Phase II metabolism by conjugation. Excretion of naproxen in man is mainly (≥95%) by urinary pathway in the form of glucuronic acid or other conjugates of native and 6-O-desmethyl naproxen. [3, 4]

Identification and characterisation	
CAS number	26159-34-2 Naproxen sodium [1] 22204-53-1 Naproxen acid [2]
Molecular weight	252.24 Naproxen sodium [1]
Brand name	Naprosyn, Naprosyn Entero
Stability/degradation (Naproxen acid)	
Ready biodegradability	not readily, literature; readily, own data [5]
Inherent biodegradability	10% 13 d, >60% 17 d, 98% 28 d; OECD 302C [2]
Other degradation information	~67 (0–99)% removal/biodegradation in sewage works, literature [5] t½ surface waters (Aug–Oct, Switzerland) = 14 d [6]
Photodegradation	90% 72 h, algal medium, algal light cabinet, OECD 201 [5]
Hydrolysis	no hydrolysable bonds
Accumulation/adsorption (Naproxen acid)	
logPow (pH < 2.18!)	3.18 [2]
logD (pH 6.5)	0.98–1.06 [7]
logD (pH 7.4)	0.23–0.33 [8, 9]
K_{OC}	<=727 pH sensitive QSAR
Sorption	no significant sorption in actual sewage works [10]
BCF	<10; <80 pH sensitive QSAR
Physico-chemical properties	
Aqueous solubility	250000 mg/l Naproxen-Na 15.9 mg/l Naproxen acid [2]

Identification and characterisation	
Dissociation constant, pK_a	4.15 Naproxen acid [2]
Melting point	255 °C [2]
Vapour pressure	ND
Boiling point	ND
K_H	3.39*E–10 atm*m3/mol QSAR Naproxen acid
Ecotoxicological data (Naproxen acid)	
Algal growth inhibition	31.82 mg/l 72h EbC50 ISO8692 *P seudokirchneriella subcap.* [11]
	21/39 mg/l 72h Eb/rC50 OECD201 *Desmodesmus subspicatus* [5]
	3.9 mg/l 72h NOEC OECD 201 *D. subspicatus* [5]
Daphnia acute immobilisation	37 mg/l 48h EC50 OECD 202 *Dap hnia magna* [5]
	10 mg/l 48h NOEC OECD 202 *D. magna* [5]
	0.032 mg/l 8d NOEC ECM *Cerioda phnia dubia chronic* [12]
Fish acute toxicity	52 mg/l 96h LC50 OECD 203 *Onc orhynchus mykiss* [5]
	32 mg/l 96h NOEC OECD 203 *O. mykiss* [5]
Micro-organism inhibition	30 mg/l 14d NOEC OECD302C activated sludge [5]
Aquatic macrophytes inhibition	24.2 mg/l 7d EC50 *Lemn* a, Naproxen-Na [5]

Identification and characterisation	
PBT/vPvB Assessment	
P: Freshwater half-life	14 d, based on measured half-life in Swiss lake [6]
Sediment half-life	d, based on
Persistence criteria fulfilled?	**not P**
B: BCF (experimental)	
alternatively, base or acid?	a
alternatively, $logD_{OW}$(p H 7)	0.329387, logDow < 3 [7, 8, 9]
Bioaccumulation criteria fulfilled?	**no significant bioaccumulation potential**
T: chronic NOEC < 0.01 mg/l?	no data on T
CMR substance?	n not CMR [1, 2]
Endocrine-disrupting effects?	no data on ED
T criteria fulfilled?	**no or incomplete data on T criteria**
PBT Assessment:	**not PBT**
Initial PEC according to fass.se	
Annual use in Sweden, *A*:	11893.6 kg/a [information from LIF 2010]
Excretion	
Excretion as parent	70 % (if not filled in/unknown, 100% is assumed by default)
Excretion as metabolite 1	30 %, with 100 % pharmacological activity compared to parent
Excretion total, *E*:	100 %, calculated as pharmacological activity of parent

Identification and characterisation	
Removal rate in STP, *R*:	67 %, based on literature data [5]
PEC = 1.5*10E–6*A*(E/100)*(100 –R) =	**0.5887 µg/l**
Initial PNEC according to EU TGD	
Lowest ecotox effect value, LEEV:	0.032 mg/l chronic NOEC *Cerioda phnia*
Assessment factor, AF:	50 chronic NOECs for algae and daphnids available
PNEC = LEEV/AF=	**0.64 µg/l**
PEC/PNEC ratio	**0.920 0.1 <PEC/PNEC <= 1**
PBT Assessment	***not PBT***

References

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Note

ND = no data; QSAR = QSAR-modelled (EPISuite, SPARC, ACD Solaris); AMC = average measured concentration; ECM = Environment Canada method; NC = nominal concentration; SC = saturation concentration.