

Seloken[®]

M R (F)

Recordati

Tablett 50 mg

(vita, runda med skåra, märkta A/BB, 8 mm)

Beta-receptorblockerare

Aktiv substans:

Metoprolol

ATC-kod:

C07AB02

Läkemedel från Recordati omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Metoprolol

Miljörisk: Användning av metoprolol har bedömts medföra låg risk för miljöpåverkan.

Nedbrytning: Metoprolol är potentiellt persistent.

Bioackumulering: Metoprolol har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.37 \cdot 10^{-6} \cdot A(100 - R)$$

$$\text{PEC} = 1.61 \mu\text{g/L}$$

Where:

A = 11 786.21 kg (total sold amount API in Sweden year 2020, data from IQVIA).

R = Removal rate = 0% (no data available)

P = number of inhabitants in Sweden = $10 \cdot 10^6$

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: Whilst metoprolol is extensively metabolised in humans, little is known about the ecotoxicity of the metabolites. Hence, as a worst case, for the purpose of this calculation, it is assumed that 100% of excreted metabolites have the same ecotoxicity as parent metoprolol.)

Excretion (metabolism)

Metoprolol is extensively metabolised in the body, with only a minor fraction (approximately 5%) excreted as the parent drug. The main route for excretion is via the urine (Ref. 2).

Ecotoxicity data

Endpoint	Species	Common Name	Method	Time	Result	Ref
E _r C50 - Based on Average Specific Growth Rate	<i>Desmod esmus subspica tus</i>	Green Alga	92/69/EE C Annex V C.3	72 h	7.3 mg/L Note 2, 3	3
NOEC - Based on Areas Under the Growth Curve					7.5 mg/L Note 1,2	
LOEC - Based on Areas Under the Growth Curve					15 mg/L Note 1,2	
E _b C50 - Based on Areas Under the Growth Curve					22.8 mg/L Note 1,2	
	<i>Pseudoki rchneriel</i>					

Endpoint	Species	Common Name	Method	Time	Result	Ref
NOEC - Based on Logarithmic Growth Rate	<i>Ia subcapitata</i>	Green Alga	OECD 201	72 h	7.5 mg/L Note 1,2	4
LOEC- Based on Logarithmic Growth Rate					15 mg/L Note 1,2	
E _r C50 - Based on Logarithmic Growth Rate					58.3 mg/L Note 1,2	
EC50 - Based on Immobilisation	<i>Daphnia magna</i>	Giant Water Flea	OECD 202	48 h	>120 mg/L Note 1,2	5
NOEC - Based on Immobilisation					30 mg/L Note 1,2	

Endpoint	Species	Common Name	Method	Time	Result	Ref
EC50	<i>Ceriodaphnia dubia</i>	Cladoceran	EPA 600/490/027	48 h	45.3 mg/L	6
LC50	<i>Oncorhynchus mykiss</i>	Rainbow Trout	OECD 203	96 h	130 mg/L Note 1,2	7
NOEC - Based on Symptoms of Toxicity					32 mg/L Note 1,2	
LC50	<i>Danio rerio</i>	Zebra Fish	OECD 203	96 h	167 mg/L Note 1,2	8
LOEC - Based on Mortality					157.5 mg/L Note 1, 2	
EC50 - Based on Respiration Inhibition	-	-	OECD 209	3 h	>100 mg/L Note 1,4	9
NOEC - Based on Respiration Inhibition				3 h	100 mg/L Note 1, 4	

Note1: Studies were conducted with metoprolol succinate, the difference in reported and actual concentrations of metoprolol is anticipated to have negligible impact on this assessment.

Note 2: Concentrations were confirmed by analysis, and results expressed as nominal.

Note 3: Data for metoprolol taken from Cleuvers M. Initial Risk Assessment for Three Beta-Blockers Found in the Aquatic Environment. *Chemosphere*, 2005, **59**, 199-205. Concentrations of metoprolol were as free base in this study.

Note 4: Results are expressed as nominal concentrations.

Predicted No Effect Concentration (PNEC)

Short-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines.

Therefore, the PNEC is based on the acute toxicity to green alga (*Desmodemus subspicatus*), the most sensitive species, and an assessment factor of 1000 is applied, in accordance with ECHA guidance (Ref. 10).

$$\text{PNEC} = 7300 \mu\text{g/L} / 1000 = 7.3 \mu\text{g/L}$$

Environmental risk classification (PEC/PNEC ratio)

$\text{PEC/PNEC} = 1.6/7.3 = 0.22$, i.e. $\text{PEC/PNEC} \leq 1$ which justifies the phrase 'Use of metoprolol has been considered to result in low environmental risk.'

In Swedish: 'Användning av metoprolol har bedömts medföra låg risk för miljöpåverkan' under the heading "Miljörisk".

Environmental Fate Data

Endpoint	Method	Test Substance Concentration	Time	Result	Ref
Partition Coefficient Octanol Water	OECD 107	100 mg/L	-	Log P = -0.06 @ pH 5 Log P = -0.90 @ pH 7	11
Percentage DOC removal	ISO 7827-1984 (E)	34 mg DOC/L	28 d	14 %	8

Degradation

Biotic degradation

The aerobic biodegradation was determined in accordance with ISO 7827-1984 (E) (Ref. 8), using the OECD guidelines' criteria for ready biodegradation. According to the results, metoprolol is not readily biodegradable (loss of Dissolved Organic Carbon (DOC) <70% after 28 days). Based on the data above (considering that no other data is available), the statement 'Metoprolol is potentially persistent' is justified.

In Swedish: 'Metoprolol är potentiellt persistent' under the heading "Nedbrytning".

Bioaccumulation

Log P = < 4 at pH 7.

Metoprolol has no significant bioaccumulation potential, as indicated by the Log P. Therefore, the statement 'Metoprolol has low potential for bioaccumulation' is used.

In Swedish: 'Metoprolol har låg potential att bioackumuleras' under the heading "Bioackumulering".

Physical Chemistry Data

Endpoint	Method	Test Conditions	Result	Reference
Solubility Water	Not specified, method unknown	-	200 mg/L	9

References

1. [ECHA] European Chemicals Agency. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.16: Environmental exposure assessment (version 3.0). February 2016.
http://echa.europa.eu/documents/10162/13632/information_requirements
2. Logimax Investigators Brochure, Edition 2 Section 5 Effects in Humans. November 2006.
3. Aquatic Ecotoxicity of Pharmaceuticals Including the Assessment of Combination Effects. Cleuvers M. *Toxicology Letters 2003 v142 n3 p185 - 194*.
4. Metoprolol Succinate: Toxicity to the green alga *Selenastrum capricornutum*. Brixham Environmental Laboratory, AstraZeneca, UK, Report BL7587. October 2003.

5. Metoprolol Succinate: Acute toxicity to *Daphnia magna*. Brixham Environmental Laboratory, AstraZeneca, UK, Report BL7588. October 2003.
6. Prediction and Experimental Validation of Acute Toxicity of Beta Blockers in *Ceriodaphnia dubia*. Fraysse B et al. *Environ. Toxicol. Chem* 2005 v24 n10 p2470 – 2476.
7. Metoprolol Succinate: Acute toxicity to rainbow trout (*Oncorhynchus mykiss*). Brixham Environmental Laboratory, AstraZeneca, UK, Report BL7589. October 2003.
8. Environmental assessment of the pharmaceutical agent "A004" from AB Astra. Report No: 4/92, Toxicon. April 1992.
9. Metoprolol Succinate: Effect on the respiration rate of activated sludge. Brixham Environmental Laboratory, AstraZeneca, UK, Report BL7772. December 2003.
10. ECHA, European Chemicals Agency. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R10. May 2008.
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11. Metoprolol Succinate: Determination of n-octanol-water partition coefficient. Brixham Environmental Laboratory, AstraZeneca, UK, Report BL7827. September 2004.