

## Cibadrex

**M****Novartis**

TABLETTER 5/6,25 mg

Avregistreringsdatum: 1998-07-31 (Tillhandahålls ej)

**Aktiva substanser:**

Benazepril

Hydroklortiazid

**ATC-kod:**

C09BA07

För information om det avregistrerade läkemedlet omfattas av Läkemedelsförsäkringen, kontakta Läkemedelsförsäkringen.

Läs mer om avregistrerade läkemedel

## Miljöpåverkan

### Hydroklortiazid

Miljörisk: Användning av hydroklortiazid har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Hydroklortiazid bryts ned långsamt i miljön.

Bioackumulering: Hydroklortiazid har låg potential att bioackumuleras.

### Detaljerad miljöinformation

#### Environmental Risk Classification

#### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.5 \cdot 10^{-6} \cdot A \cdot (100 - R) = 0.42 \mu\text{g/L}$$

Where:

A = 2789.28 kg (total sold amount API in Sweden year 2016, data from QuintilesIMS).

R = 0 % removal rate.

P = number of inhabitants in Sweden =  $9 \cdot 10^6$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

## Predicted No Effect Concentration (PNEC)

### Ecotoxicological studies

*Algae (Pseudokirchneriella subspicata)* (OECD201) (NOTOX Project 490915):

EC50 72 h (growth rate) > 100.0 mg/L

NOEC 72 h = 100.0 mg/L

*Crustacean (Daphnia magna, waterflea):*

Acute toxicity

EC50 48 h (immobilisation) > 100.0 mg/L (OECD202) (Ciba-Geigy Test No: 948032)

Chronic toxicity

NOEC 21 days (reproduction, survival and parental length) = 100 mg/L; no effect up to the highest concentration tested (OECD 211) (NOTOX Project 485928)

*Fish:*

Acute toxicity (*Danio rerio*, zebra fish)

LC50 96 h (mortality) > 100.0 mg/L (OECD203) (Ciba-Geigy Test No. 811678)

Chronic toxicity (*Pimephales promelas*, fathead minnow)

NOEC 30 days (hatchability, survival, length and weight) = 10.0 mg/L; no effect up to the highest concentration tested (OECD 210) (NOTOX Project 485928)

*Other ecotoxicity data:*

Bacterial respiration inhibition

EC<sub>50</sub> 3 h > 750 mg/L (activated sludge respiration inhibition) (OECD209) (Ciba-Geigy Test No. 948033)

Sediment-dwelling organisms (*Chironomus riparius*, non-biting midge)

NOEC 28 days (emergence rate and development rate) = 10.0 mg/L (OECD 218) (Report No BR0137/B)

PNEC derivation:

PNEC = 1000 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for fish early life stage toxicity has been used for this calculation.

### Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.42 µg/L / 1000 µg/L = 0.00042, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of hydrochlorothiazide has been considered to result in insignificant environmental risk."

### Degradation

#### Biotic degradation

*Ready degradability:*

36.0 % degradation in 28 days, not readily biodegradable (OECD301E). (Report No. BR0030/B)

*Simulation studies:*

DT<sub>50</sub> (total system) = 34.7 - 37.3 days (OECD 308). (Report No. BR0040/B)

Sediments were extracted with 100 ml of methanol by agitating for at least 12 hours. This was followed by a further extraction with 100 ml of 90% ethanol.

A significant amount of mineralisation occurred throughout the study. At the end of the study  $^{14}\text{CO}_2$  accounted for 58% to 70%. Non-extractable residues in sediment accounted for 9-23% of applied radioactivity by the end of the study. Parent substance was 10-11 % of applied radioactivity by the end of the study.

#### *Justification of chosen degradation phrase:*

According to the pass criteria for OECD308 studies, hydrochlorothiazide can be classified as 'Hydrochlorothiazide is slowly degraded in the environment' ( $\text{DT}_{50}$  for total system <120days)

#### **Bioaccumulation**

##### *Partitioning coefficient:*

$\text{Log } D_{\text{ow}} = 0.09$  at pH 7 (OECD107). (NOTOX Project 490916)

##### *Justification of chosen bioaccumulation phrase:*

Since  $\text{log } D_{\text{ow}} < 4$  at pH 7, hydrochlorothiazide has low potential for bioaccumulation.

#### **Excretion (metabolism)**

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. Within 72 hours, 60-80% of a single oral dose is excreted in the urine, 95% in unchanged form, and about 4% as the hydrolysate 2-amino-4-chloro-m-benzenedisulfonamide (ACBS). Up to 24% of an oral dose may be found in the feces, and a negligible amount is excreted via the bile. (ESIDREX<sup>®</sup> (hydrochlorothiazide) Core Data Sheet)

#### **PBT/vPvB assessment**

Hydrochlorothiazide is slowly degraded and has low potential for bioaccumulation based on the screening criteria for B and can therefore not be considered a potential PBT substance.

#### **References**

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.  
[http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
- NOTOX Project 490915. Fresh water algal growth inhibition test with HCTZ DS. Final report: 09 October 2009.
- Ciba-Geigy Test No: 948032. Report on the acute toxicity test of PBS 000397.1 on Daphnia. Final report: 27 January 1995.
- NOTOX Project 485927. *Daphnia magna*, reproduction test with HCTZ DS (semi-static). Final report: 09 November 2007.
- Ciba-Geigy Test No: 811678. Full report / full reference not available.
- NOTOX Project 485928. Fish early-life stage toxicity test with HCTZ DS (semi-static). Final report: 09 November 2008.
- Ciba-Geigy Test No. 948033. Report on the test for activated sludge respiration inhibition of PBS 000397.1. Final report: 21 October 1994.
- Report No BR0137/B. [ $^{14}\text{C}$ ] hydrochlorothiazide: Determination of the effects in a water-sediment system on the emergence of *Chironomus riparius* using spiked sediment. Final report: 03 March 2010.
- Report No BR0030/B. [ $^{14}\text{C}$ ]Hydrochlorothiazide: 28 day ready biodegradation. 06 October 2009.
- Report No BR0040/B. HYDROCHLOROTHIAZIDE: Aerobic Transformation in Aquatic Sediment Systems. Final report: 02 February 2010.

- NOTOX Project 490916. Determination of the partition coefficient (n-octanol/water) of HCTZ DS. Final report: 01 July 2009.
- ESIDREX<sup>®</sup> (hydrochlorothiazide) Core Data Sheet Version 2.0. September 2014.