

Mimpara

M R F_f

Amgen

Filmdragerad tablett 30 mg

(Ljusgrön, oval (cirka 9,7 mm lång och 6,0 mm bred), filmdragerad tablett märkt "AMG" på ena sidan och "30" på den andra)

medel som reglerar kalciumomsättningen,
anti-paratyreoideamedel

Aktiv substans:

Cinakalcet

ATC-kod:

H05BX01

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

Miljöpåverkan

Cinakalcet

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

Nedbrytning: Cinakalcet är potentiellt persistent.

Bioackumulering: Cinakalcet har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC ratio

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula (1):

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

$$\text{PEC} = 0.0047 \text{ ug/L}$$

Where:

A = 31.69 kg (total sold amount API in Sweden year 2017, data provided by IQVIA).

R = X % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available. The value 0 is used here.

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

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (2)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (2)

Predicted No Effect Concentration (PNEC)

The PNEC value was calculated based on the NOEC for algal growth inhibition and reproductive toxicity to *Daphnia Magna* i.e. 0.025 mg/L (see table 1 below). An Assessment Factor (AF) of 50 was used which resulted in a PNEC value of 0.5 ug/L.

This means that the PNEC/PEC ratio obtained was $0.0047/0.5 \text{ ug/L} = 0.007$ which would translate into the following environmental risk phrase:

“Användningen av cinakalcet har bedömts medföra försumbar risk för miljöpåverkan”

Please find below a summary of the available data on effects on aquatic organisms.

Table 1. Summary of Studies on the Effects on Aquatic Organisms

Study	Result
Acute Effects on the <i>Pimephales Promelas</i> (Feathead Minnow) (3)	24 hour LC50 = 0.183 mg/L 48 hour LC50 = 0.125 mg/L 72 hour LC50 = 0.089 mg/L 96 hour LC50 = 0.085 mg/L 96 hour EC05 / LOEC = 0.063 mg/L
Acute Toxicity to <i>Daphnia Magna</i> (OECD 202) (4)	24 hour EC50 = 0.23 mg/L (measured) 48 hour EC50 = 0.16 mg/L (measured) 48 hour NOEC = 0.049 mg/L (measured)
Respiratory Inhibition Test Using Activated Sludge (OECD 209) (5)	3 hour EC20 = 15.4 mg/L 3 hour EC50 = 36.6 mg/L NOEC = 1 mg/L
Algal Growth Inhibition Study (<i>Selenastum capricornutum</i>) (OECD 201) (6)	72- and 96-hour EC50 = 0.0191 and 0.0175 mg/L (cell numbers) 72- and 96-hour EC50 = 0.0203 and 0.0191 mg/L (area under the growth curve)

Study	Result
	72- and 96-hour EC50 = 0.0330 and 0.0320 mg/L (growth rates) 72- and 96-hour LOEC = 0.0125 mg/L (cell numbers, area under the growth curve and growth rate) 72- and 96-hour NOEC = 0.0250 mg/L (cell numbers, area under the growth curve and growth rate)
Reproductive Toxicity to <i>Daphnia Magna</i> (OECD 211) (7)	21-day EC50 (reproductive effects) = 0.065 mg/L NOEC (reproductive effects) = 0.025 mg/L LOEC (reproductive effects) = 0.050 mg/L 21-day LC50 (mortality in parents) = 0.14 mg/L NOEC (mortality in parents) = 0.10 mg/L LOEC (mortality in parents) = 0.20 mg/L

Biodegradation

Two environmental fate assays to assess the potential for cinacalcet hydrochloride to biodegrade in water were initially conducted (8, 9).

This was followed by an assessment of the anaerobic and aerobic degradation in sediment OECD Method 308 (10). However, under the conditions of the test, recovery from the sediment was not

achievable to the requirements of the OECD Method (70% recovery).

(Table 2) summarizes the environmental fate studies described above:

Test	Result
Instrumental Respirometric Method to Determine Biodegradability /Inhibition/Toxicity (8)	Under the conditions of the study, cinacalcet did not appear to biodegrade based on respirometric measurements.
Sealed Vessel CO ₂ Production Test (9)	The test substance is not readily biodegradable under the study criteria. Cinacalcet did not pass the criteria of greater than 60% of the theoretical carbon dioxide production that would indicate a readily biodegradable compound within the 10-day test duration.
Aerobic and Anaerobic Degradation Transformation in Aquatic Systems (OECD 308) (10, 11)	Under the conditions of the test, recovery from the sediment was not achievable to the requirements of the OECD Method (70% recovery).

Based on these data and the physical-chemical properties described in Table 3 below the following summary phrase for degradation has been chosen:

“Cinacalcet är potentiellt persistent.”

Bioaccumulation

No Bioconcentration Factor (BCF) study was performed. In the absence of a measured BCF value, the bioaccumulation potential may be indicated from $\log K_{ow}$ and $\log D_{ow}$ (see table 3 below). $\log K_{ow}$ is 4.79 which indicates that the substance may bioaccumulate to a high degree. For complex ionizable molecules, such as cinacalcet, it may be more relevant to use $\log D_{ow}$ at pH 7. $\log D_{ow}$ values equal to or greater than 4 indicate that the chemical may bioconcentrate or sorb significantly but as $\log D_{ow}$ is below 4 (3.53) this would rather indicate that cinacalcet has a low potential to bioaccumulate. Based on the $\log D_{ow}$ value the following phrase has been chosen:

”Cinacalcet har låg potential att bioackumuleras.”

Table 3: Physical and Chemical Properties of Cinacalcet of Relevance to Environmental Fate and Effect (12)

Physical-Chemical Property	Value or Determination
pKa	8.72 as determined by potentiometric titration
pH of aqueous solution	5.1 (saturated at 25 °C)
Solubility profile	Sparingly soluble in water (1.5 mg/ml @ pH 5; <0.01 mg/ml @ pH 7) Slightly soluble in acetonitrile; freely soluble in methanol, ethanol, methylene chloride, and chloroform; very slightly soluble in hexane; sparingly soluble in isopropyl alcohol

Physical-Chemical Property	Value or Determination
Partition coefficient (octanol:water)	$\log K_{ow} = 4.79$ at 25 °C
UV spectroscopy	Absorbance maxima at 314 nm Photolysis is not a potential degradation pathway, i.e., does not absorb in UV spectrum wavelengths
Adsorption coefficient (K_{oc})(calculated)	$\log K_{oc} = 4.03$ Calculation by the equation $\log K_{oc} = 0.554 \log K_{ow} + 1.337$
Octanol-water distribution coefficient (D_{ow}) (calculated)	$\log D_{ow} = 3.53$ Calculation by the following equation $K_{ow} = D_{ow} (1 + 10^{(\text{abs}(\text{pH} - \text{pKa}))})$

References:

1. FASS, (2012). Environmental classification of pharmaceuticals in www.fass.se – guidance for pharmaceutical companies.
2. ECHA, (2008). Guidance on Information Requirements and Chemical Safety Assessment. Helsinki, Finland: European Chemicals Agency.
3. Acute Effects on the Fathead Minnow *Pimephales Promelas*. Aqua Survey Inc. Report Study No. 2000-121-003, 2001.
4. Acute Effects on *Daphnia Magna*, Study No. 162774070-300, (Conducted by Stantec Inc., Guelph, Ontario, Canada), 2004.

5. Respiratory Inhibition Test, Study No. 2-11-0938A, (Conducted by Vizon SciTec Inc, Vancouver, British Columbia, Canada), 2004.
6. Algal Growth Inhibition Study, Study ID No. 162774070-200, (Conducted by Stantec Inc., Guelph, Ontario, Canada), 2004.
7. Reproductive Toxicity to *Daphnia Magna*, Study No. 162774070-400, (Stantec Inc., Guelph, Ontario, Canada), 2004.
8. Instrumental Respirometric Method to Determine Biodegradability / Inhibition/Toxicity – Study No. 2000-121-002, (Conducted by Aqua Survey, Inc., Flemington, New Jersey), 2001.
9. Sealed Vessel CO₂ Production Test. Study No. 2000-121-001 (Aqua Survey, Inc, Flemington, New Jersey), 2001.
10. OECD Guidelines for the Testing of Chemicals, aerobic, Anaerobic Degradation Transformation in Aquatic Systems. Guideline 308, 2002.
11. Aerobic and Anaerobic Degradation Transformation in Aquatic Systems Study No. 2-11-0938, (Conducted by Vizon SciTec Inc, Vancouver, British Columbia, Canada), 2005.
12. Data on file - Amgen Environmental Classification Report dated April 18, 2012.