

## Plaquenil®

**M R F****Sanofi AB**

Film-dragerad tablett 200 mg

(vita, kupade, film-dragerade, märkta med HCQ på ena sidan och 200 på den andra, 9,7 mm)

Antireumatikum

**Aktiv substans:**

Hydroxiklorokin

**ATC-kod:**

P01BA02

Läkemedel från Sanofi AB omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Hydroxiklorokin

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

Nedbrytning: Hydroxiklorokin är potentiellt persistent.

Bioackumulering: Hydroxiklorokin har låg potential att bioackumuleras.

# Detaljerad miljöinformation

## Environmental Risk Classification

### *Predicted Environmental Concentration (PEC)*

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.097 \mu\text{g/L}$$

Where:

A = 647.1789 kg (total sold amount API in Sweden year 2018, data from IQVIA)

R = 0% removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)

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

V (L/day) = volume of wastewater per capita and day = 200 (Ref I)

D = factor of dilution of waste water by surface water flow = 10 (Ref I)

### *Predicted No Effect Concentration (PNEC)*

*Ecotoxicological studies*

*Hydroxychloroquine*

*Algae (Pseudokirchneriella subcapitata):*

EC<sub>50</sub> 72 h (growth rate): 3110 μg/L

EC<sub>10</sub> 72 h (growth rate): 1830 µg/L

NOEC 72 h (growth rate): 768 µg/L

Protocol: OECD 201

(Ref II)

*Crustacean (Daphnia magna):*

EC<sub>50</sub> 48 h (immobilization): 14000 µg/L

NOEC 48 h (immobilization): 6760 µg/L

Protocol: OECD 202

(Ref III)

*Hydroxychloroquine Sulfate*

*Algae (Pseudokirchneriella subcapitata):*

EC<sub>50</sub> 72 h (growth rate): 3570 µg/L

EC<sub>10</sub> 72 h (growth rate): 1950 µg/L

NOEC 72 h (growth rate): 183 µg/L

Protocol: OECD 201

(Ref IV)

*Crustacean (Daphnia magna):*

EC<sub>10</sub> 21 d (reproduction): 173 µg/L

NOEC 21 d (reproduction): 85.8 µg/L

Protocol: OECD 211

(Ref V)

*Fish (Danio Rerio):*

LC<sub>50</sub> 96 h (lethality): > 100000 µg/L

NOEC 96 h (lethality): > 100000 µg/L

Protocol: OECD 236

(Ref VI)

*Other ecotoxicity data:*

PNEC = Lowest NOEC/50:

Lowest NOEC:

*Crustacean (Daphnia magna):*

NOEC 21 d (reproduction): 85.8 µg/L

PNEC: 1.716 µg/L

***Environmental Risk Classification (PEC/PNEC ratio)***

PEC/PNEC: 0.097/1.716 = 0.0565

PEC/PNEC ≤ 0.1: Use of hydroxychloroquine has been considered to result in insignificant environmental risk.

**Degradation**

***Biotic degradation***

*Hydroxychloroquine*

Test showed 0% degradation in 28 days.

(Ref VII)

Hydroxychloroquine is therefore potentially persistent.

## ***Abiotic degradation***

Literature data indicates photochemical decomposition reactions.  
(Ref VIII)

## **Bioaccumulation**

*Partitioning coefficient:*

Log D (pH 7.4) = 0.62 (method: experimentally obtained by Sirius GLpK automated computerized potentiometric system) (Ref IX)

*Justification of chosen bioaccumulation phrase:*

Since log D is < 4 at pH 7.4, the substance has low potential for bioaccumulation.

## **Excretion**

The metabolism of chloroquine and hydroxychloroquine differs only in that the latter drug gives two first-stage metabolites, whereas chloroquine gives one. Oral absorption of both drugs in man is nearly complete. However, three times as much chloroquine as hydroxychloroquine appears in the urine, and three times as much hydroxychloroquine as chloroquine appears in the feces (Ref X). Chloroquine is extensively metabolized in the liver. Chloroquine and its metabolites are excreted in the urine with about half of a dose appearing as unchanged drug (Ref XI).

## **References**

- I. ECHA, European Chemicals Agency, 2008 Guidance on information requirements and chemical safety assessment.  
[http://guidance.echa.europa.eu/docs/guidance\\_document/informa](http://guidance.echa.europa.eu/docs/guidance_document/informa)
- II. Sanofi Internal report: HYDROXYCHLOROQUINE (CAS N°118-42-3) ALGAL GROWTH INHIBITION TEST

(PSEUDOKIRCHNERIELLA SUBCAPITATA). OECD 201. Report BPL15-0032 EAA , June 2016.

- III. Sanofi internal report: HYDROXYCHLOROQUINE (CAS N°118-42-3) DAPHNIA MAGNA, ACUTE IMMOBILISATION TEST. OECD 202. Report BPL15-0032 EDA, June 2016.
- IV. Sanofi Internal report: Hydroxychloroquine Sulfate (CAS N° 747-36-4): Toxicity to Pseudokirchneriella subcapitata in an Algal Growth Inhibition Test. OECD 201. Report 135551210, March 2019
- V. Sanofi Internal report: Hydroxychloroquine Sulfate (CAS N° 747-36-4): Influence to Daphnia magna in a Semi-Static Reproduction Test. OECD 211. Report 135551221, February 2019.
- VI. Sanofi internal report: Hydroxychloroquine Sulfate (CAS N° 747-36-4): Acute Toxicity to Zebrafish (Danio rerio) Embryos in a 96-hour Static Test. OECD 236. Report 127671238, July 2018.
- VII. Sanofi internal report: HYDROXYCHLOROQUINE (CAS N°118-42-3) READY BIODEGRADABILITY “MANOMETRIC RESPIROMETRY. OECD 301F. Report BPL15-0032 EB, June 2016.
- VIII. Tonnesen H., Grislingaas A.L., Woo S.O. and Karlsen J. 1988, Photochemical stability of antimalarials. I. Hydroxychloroquine, International Journal of Pharmaceutics, 43, 215-219.
- IX. Warhurst, D.C. et al. Hydroxychloroquine is much less active against chloroquine-resistant Plasmodium falciparum, in agreement with its physicochemical properties. Journal of Antimicrobial Chemotherapy (2003) 52, 188 - 193.
- X. McChesney, E.W., 1983, Animal toxicity and pharmacokinetics of Hydroxychloroquine sulfate. American Journal of Medicine. 75: 1, 11-18.

**XI.** Product Information: ARALEN(R) oral tablet, chloroquine phosphate oral tablet, USP. Sanofi-Synthelabo Inc, New York, NY, 2003