

## Revolade

M R F<sub>f</sub>

### Novartis

Filmdragerad tablett 25 mg

(Rund, bikonvex, vit filmdragerad tablett (cirka 10,3 mm i diameter) stansad med "GS NX3" och "25" på en sida.)

Hemostatika

### Aktiv substans:

Eltrombopag

### ATC-kod:

B02BX05

Läkemedel från Novartis omfattas av Läkemedelsförsäkringen.

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

## Miljöpåverkan

### Eltrombopag

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

Nedbrytning: Eltrombopag är potentiellt persistent.

Bioackumulering: Eltrombopag har låg potential att bioackumuleras.

### Detaljerad miljöinformation

### Detailed background information

### Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

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

$$\text{PEC} = 0.00103 \mu\text{g/L}$$

Where:

A = 7.5272 kg (total sold amount API in Sweden year 2021, data from IQVIA).

R = 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)

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

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

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

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

#### **Ecotoxicological studies**

*Lesser Duckweed (Lemna minor):*

IC50 96h (inhibition growth rate) = 1'200 µg/L (OECD 221) (Reference 3)

NOEC = 450 µg/L

*Water flea (Daphnia magna)*

#### **Acute toxicity**

EC50 48 h (immobility) = 1'500 µg/L (OECD 202) (Reference 4)

NOEC = 540 µg/L

#### **Chronic toxicity**

NOEC 21 d (reproduction and immobilisation) = 120 µg/L (OEC 211) (Reference 5)

*Fish:*

**Acute toxicity** in rainbow trout (*Oncorhynchus mykiss*)

LC50 96 h (lethality) = 2'500 µg/L (OECD 203) (Reference 6)

NOEC = 1'600 µg/L

**Chronic toxicity** in zebra fish (*Danio rerio*)

NOEC 28 d (larval survival, and length and weight) = 52.0 µg/L (Reference 7)

*Other ecotoxicity data:*

*Microorganisms in activated sludge:*

EC50 3 h (inhibition) > 320'000 µg/L @ 3 hrs (OECD 209) (Reference 8)

NOEC = 25'000 µg/L

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

NOEC 28 days (development rate and emergence) = 104.0 mg/kg (OECD 218) (Reference 9)

PNEC = 52 µg/L / 10 = 5.2 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three chronic NOECs. The NOEC for fish larval survival and fish larval growth (= 52 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

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

PEC/PNEC = 0.00103 µg/L / 5.2 µg/L = 0.000198, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of eltrombopag has been considered to result in insignificant environmental risk."

### **Degradation**

#### **Biotic degradation**

*Ready degradability:*

No data

*Inherent degradability:*

10% degradation in 14 days (OECD 302). (Reference 10)

This substance is not inherently biodegradable.

*Transformation in water-sediment systems:*

DT50 in total system > 120.0 days (OECD 308). (Reference 11)

Study duration: 106 days;

Due to rapid degradation in the water and extended lag phases in both test systems approximately 10 to 20 % degradation of Eltrombopag Olamine was observed over too few data points to allow kinetics to be performed. Therefore, no DT50 values were calculated for the water phases, sediment or the entire system, respectively.

### **Abiotic degradation**

*Hydrolysis:*

50% degradation @14°C in 14 days (pH 7) (TAD 3.09). (Reference 12)

50% degradation @14°C in 752 days (pH 9)

*Photolysis:*

No data

*Justification of chosen degradation phrase:*

Eltrombopag is not readily biodegradable nor inherently biodegradable. This substance is predicted to degrade via hydrolysis and the half-life is less than 40 days. However, the results from the hydrolysis study were not strongly first order and rates did not scale according to temp. The phrase "Eltrombopag is potentially persistent" is thus chosen.

### **Bioaccumulation**

*Bioconcentration Factor (BCF)*

*Rainbow trout, Oncorhynchus mykiss*

BCF<sub>ss</sub> = 14 (OECD 305) (Reference 13)

BCF<sub>k</sub> = 16-29

*Partitioning coefficient:*

Log Dow = 1.54 at pH 7.4 (OECD 107) (Reference 14)

Log Dow at pH 1.2 = -0.6

Log Dow at pH 6.0 = -0.1

Log Dow at pH 7.4 = 1.54

*Justification of chosen bioaccumulation phrase:*

Since BCF < 500, the substance has low potential for bioaccumulation.

### **Excretion (metabolism)**

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon AUC<sub>0-</sub>. Minor metabolites due to glucuronidation and oxidation were also detected. In vitro studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours (Reference 2).

### **PBT/vPvB assessment**

Eltrombopag does not fulfil the criteria for PBT and/or vBvP.

All three properties, i.e. 'P', 'B' and 'T' are required in order to classify a compound as PBT (Reference 1).

Eltrombopag does not fulfil the criteria for PBT and/or vBvP based on a BCF  $\leq$  2000.

## References

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5. Report 2014N194420\_00: Eltrombopag Olamine: Effect on Survival and Reproduction of Daphnia magna in a Semi-Static Test over Three Weeks (OECD 211) (Project Number D80342). Harlan Laboratories, March 2014.
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