

Erivedge

M R EF

Roche

Kapsel, hård 150 mg

(Rosafärgad ogenomskinlig underdel märkt "150 mg" och grå ogenomskinlig överdel märkt "VISMO" med svart bläck.

Kapselstorleken är 'storlek 1' (dimensioner 19,0 x 6,6 mm).)

Antineoplastiska medel

Aktiv substans:

Vismodegib

ATC-kod:

L01XX43

Läkemedel från Roche omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Vismodegib

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

Nedbrytning: Vismodegib är potentiellt persistent.

Bioackumulering: Vismodegib har låg potential att bioackumuleras.

Detaljerad miljöinformation

Identification and characterisation

Chemical name: Vismodegib

CAS number: 879085-55-9 [1]

Molecular weight: 421.31 [1]

Remark: -

Brand name: Erivedge [1]

Physico-chemical properties

Aqueous solubility: 0.879 mg/l (20 °C) (OECD 105) [1]

Dissociation constant, pK_a : 3.4–3.5 (base) [1]

Melting point: 186–188 °C (OECD 102) [1]

Vapour pressure: ND

Boiling point: ND

K_H : 8.87×10^{-15} atm*m³/mol QSAR

QSAR = QSAR-modelled (EPISuite, SPARC, ACD Solaris)

Predicted Environmental Concentration (PEC)

PEC is calculated according to the formula:

$$\begin{aligned} \text{PEC } (\mu\text{g/L}) &= (A \times 1'000'000'000 \times (100-R)) / (365 \times P \times V \times D \times 100) \\ &= 1.5 \times 10^{-6} \times A \times (100 - R) = 0.00016 \mu\text{g/L} \end{aligned}$$

Where:

A Sold quantity = 1.0794 kg/y (total sold amount API in Sweden year 2017, data from IQVIA)

R Removal rate = 0 % Default [2]

P Population of Sweden = 9000000

V Volume of Wastewater = 200 l/day Default [2]

D Factor for Dilution = 10 Default [2]

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Green alga (*Raphidocelis subcapitata*): [3]

72 h ErC50 (growth rate) = 118 µg/l (OECD 201)

72 h ErC10 (growth rate) = 92 µg/l (OECD 201)

72 h EyC50 (yield) = 99 µg/l (OECD 201)

72 h EyC10 (yield) = 81 µg/l (OECD 201)

72 h NOEC (overall) = 69 µg/l (OECD 201)

Water-flea (*Daphnia magna*): [4]

21 d NOEC (reproduction) = 1500 µg/l (OECD 211)

Zebra fish (*Danio rerio*): [5]

35 d NOEC (overall NOEC) = 1600 µg/l (OECD 210)

Micro-organisms (activated sludge):

3 h NOEC = 1000 mg/l (OECD 209) [6]

28 d NOEC (toxicity control) = 54 mg/l (OECD 301 F) [7]

PNEC Derivation

The PNEC is based on the following data:

PNEC (mg/l) = lowest chronic NOEC/10, where 10 is the assessment factor used. A NOEC of 69 µg/l for Algae has been used for this calculation.

$PNEC = 69 / 10 = 6.9 \mu\text{g/l}$

Environmental Risk Classification (PEC/PNEC Ratio)

PEC Predicted Environmental Concentration = 0.00016 µg/L

PNEC Predicted No Effect Concentration = 6.9 µg/L

Ratio PEC/PNEC = 0.00002

PEC/PNEC = 0.00016/6.9 = 0.00002 for Vismodegib which justifies the phrase 'Use of Vismodegib has been considered to result in insignificant environmental risk.'

Degradation

Biotic Degradation

Ready biodegradability: [7]

0% after 28 days of incubation BOD/ThOD (OECD 301 F)

Inherent biodegradability: ND

Other degradation information: [8]

DT50 (water) = 3.3–3.7 d (OECD 308)

DT50 (sediment) >1 y (OECD 308)

DT50 (total system) >1 y (OECD 308)

Abiotic Degradation

Photodegradation: ND

Hydrolysis: ND

Vismodegib is not readily biodegradable; it is also not degradable in water/sediment systems. This justifies the phrase 'Vismodegib is potentially persistent.'

Bioaccumulation/Adsorption

$\log P_{OW} = 1.59$ (pH 7, non-dissociated state) (OECD 117) [9]

K_{OC} (soils) = 2129–5001 l/kg (OECD 106) [10]

K_{OC} (sludges) = 684–895 l/kg (OECD 106) [10]

BCF = 54 l/kg QSAR

Vismodegib has low potential for bioaccumulation since the $\log P_{ow}$ is <4 .

Excretion/metabolism

The metabolism of vismodegib was investigated in both in vitro and in vivo investigations. The major metabolic pathways involved oxidations of the 4-chloro-3 (pyridine-2-yl)-phenyl moiety followed by sequential glucuronidation or sulfation. In mass balance studies in rat and dog, drug derived radioactivity was recovered largely in feces followed by bile. [11]

References

1. F. Hoffmann-La Roche Ltd. 2019. Safety Data Sheet for Vismodegib, 01.04.2019;
https://www.roche.com/sustainability/what_we_do/for_communities_ar.htm.
2. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment.
http://guidance.echa.europa.eu/docs/guidance_document/information_
3. Harlan Laboratories, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2011). RO5450815-000: Toxicity to *Pseudokirchneriella subcapitata* in a 72-Hour Algal Growth Inhibition Test. Harlan study no. D09861.
4. Harlan Laboratories, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2011). RO5450815-000: Effect on Survival and

Reproduction of *Daphnia magna* in a Semi-Static Test over Three Weeks. Harlan study no. D096631.

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6. Harlan Laboratories, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2010). RO5450815-000: Toxicity to Activated Sludge in a Respiration Inhibition Test. Harlan study no. C96653.

7. BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2010). PAS-RO5450815-000. Ready biodegradability - Evaluation of the aerobic biodegradability in an aqueous medium: Manometric Respirometry Test. BMG study no. A09-01583.

8. Harlan Laboratories, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2011). [14C]-RO5450815-000: Route and Rate of Degradation in Aerobic Aquatic Sediment Systems. Harlan study no. C96620.

9. BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2010). PAS-RO5450815-000. Determination of the partition coefficient between octanol and water (logPow) by high-performance liquid chromatography (HPLC). BMG study no. A09-01587.

10. Harlan Laboratories, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2011). [14C]-RO5450815-000: Adsorption/Desorption on Three Soils and Two Sludges. Harlan study no. C96618.

11. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Assessment report for Erivedge. EMA/297688/2013, 25 April 2013.