

## Esbriet

M R EF

**Roche**

Filmdragerad tablett 267 mg

(gula, ovala, cirka 1,3 x 0,6 cm bikonvexa, präglade med "PFD")

Immunsuppressiva medel, övriga immunsuppressiva medel

### Aktiv substans:

Pirfenidon

### ATC-kod:

L04AX05

Läkemedel från Roche omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Pirfenidon

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

Nedbrytning: Pirfenidon är potentiellt persistent.

Bioackumulering: Pirfenidon har låg potential att bioackumuleras.

### Detaljerad miljöinformation

#### *Identification and characterisation*

CAS number: 53179-13-8 [1]

Molecular weight: 185.22 [1]

Brand name: Esbriet [1]

#### *Physico-chemical properties*

Aqueous solubility: 17.8-18.2 mg/l water; pH 3.9 - pH 8.7 (OECD 105) [1]

Dissociation constant,  $pK_a$ : -0.20 QSAR [1]

Melting point: 106-112 °C [1]

Vapour pressure: 0.0049 Pa QSAR

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

#### *Predicted Environmental Concentration (PEC)*

PEC is calculated according to the formula:

$$\text{PEC } (\mu\text{g/l}) = (A \times 1'000'000'000 \times (100-R)) / (365 \times P \times V \times D \times 100) = 1.37 \times 10^{-6} \times A \times (100 - R) = 0.027 \mu\text{g/l}$$

Where:

A Sold quantity = 196,31789 kg/y sales data from IQVIA / LIF - kg consumption 2021

R Removal rate = 0 % [2]

P Population of Sweden = 10 000 000

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

D Factor for Dilution = 10 [2]

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

#### **Ecotoxicological Studies**

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

ErC50 72 h (growth rate) = 67.1 mg/l (OECD 201)

EyC50 72 h (yield) = 44.0 mg/l (OECD 201)

NOEC 72 h = 18.3 mg/l (OECD 201)

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

NOEC 21 days (reproduction) = 94 mg/l (OECD 211)

Fathead minnow (*Pimephales promelas*): [5]

NOEC 28 days (overall) = 10.6 mg/l (OECD 210)

Micro-organisms: [6]

NOEC 3 h (respiration inhibition) = 100 mg/l (OECD 209)

#### **PNEC Derivation**

*The PNEC is based on the following data:*

PNEC ( $\mu\text{g/l}$ ) = lowest chronic NOEC/10, where 10 is the assessment factor used. A NOEC of 10600  $\mu\text{g/l}$  for fish has been used for this calculation. [1]

$$\text{PNEC} = 10600 \mu\text{g/l} / 10 = 1060 \mu\text{g/l}$$

### ***Environmental Risk Classification (PEC/PNEC Ratio)***

PEC Predicted Environmental Concentration = 0.027  $\mu\text{g/l}$

PNEC Predicted No Effect Concentration = 1060  $\mu\text{g/l}$

Ratio PEC/PNEC = 0.000025

**PEC/PNEC = 0.027/1060 = 0.000025 for Pirfenidone which justifies the phrase 'Use of Pirfenidone has been considered to result in insignificant environmental risk.'**

### ***Degradation***

#### **Biotic Degradation**

Ready biodegradability: [7]

9% after 28 days of incubation CO<sub>2</sub>/TOC (OECD 301 B)

Other degradation information (OECD 308): [8]

DT50 (water phase): 34-46 days

DT50 (total system): 116-191 days

DT90 (water phase): 212-332 days

DT90 (total system): 386-634 days

<sup>14</sup>C<sub>2</sub>O evolution within 99 days: 4.8-10.3% of total radioactivity

Pirfenidone dissipated from the water of aquatic sediment systems with DT50 values of 34 days and 46 days. DT50 values for the dissipation of pirfenidone from the overall systems were 191 and 116 days.

Pirfenidone was degraded within both water and sediment phases and at least six metabolites were formed, none of which were of quantitative significance ( $\leq 9.5\%$  of the applied pirfenidone).

**Pirfenidone is not readily biodegradable. The DT50 in an OECD 308 study is >120 days for the total system. This justifies the phrase 'Pirfenidone is potentially persistent'.**

#### ***Bioaccumulation/Adsorption***

logK<sub>OW</sub> 0.9 pH 6.7 (OECD 107) [1]

K<sub>OC</sub> 24.0-41.3 L/kg (OECD 106) [9]

**Pirfenidone has low potential for bioaccumulation (log KOW <4).**

#### ***Excretion/metabolism***

Pirfenidone is rapidly and extensively absorbed from the gut into the systemic circulation (about 80%), where it is rapidly metabolised with a half-life of one to three hours. Pirfenidone undergoes rapid conversion to a 5-hydroxymethyl metabolite which appears to have a pharmacologic potency of about 50% of that of pirfenidone, and this in turn is rapidly oxidised to the inactive 5-carboxylic acid metabolite. Pirfenidone is mainly eliminated from the body in the urine as the hydrophilic metabolites in particular the 5-carboxylic acid metabolite (80-85% of administered <sup>14</sup>C-pirfenidone). [1]

#### ***References***

1. F. Hoffmann-La Roche Ltd (2021): Environmental Risk Assessment Summary for Pirfenidone. <https://www.roche.com/sustainability/environment/environmental-risk-assessment-downloads.htm>.
2. European Medicines Agency (EMA) (2006/2015): Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 01 June 2006, EMA/CHMP/SWP/447/00 corr 2.
3. Huntingdon Life Sciences, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2009). Pirfenidone: Algal growth inhibition assay. HLS study no. GAE0010.
4. Huntingdon Life Sciences, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2009). Pirfenidone: Prolonged Toxicity to Daphnia magna. HLS study no. GAE0011.
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7. Huntingdon Life Sciences, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2009). Pirfenidone: Assessment of ready biodegradability: Modified Sturm test. HLS study no. GAE0001.
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9. Huntingdon Life Sciences, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2009). Pirfenidone: Adsorption/Desorption on Soils & Sewage Sludge. HLS study no. GAE0015.