

## Eliquis

M R F

### Bristol-Myers Squibb

Filmdragerad tablett 5 mg

(Rosa, ovala tabletter (9,73 mm x 5,16 mm) med 894 präglat på ena sidan och 5 på den andra sidan.)

Direkt faktor Xa-hämmare

### Aktiv substans:

Apixaban

### ATC-kod:

B01AF02

Läkemedel från Bristol-Myers Squibb omfattas av Läkemedelsförsäkringen.

## Miljöpåverkan

### Apixaban

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

Nedbrytning: Apixaban bryts ned långsamt i miljön.

Bioackumulering: Apixaban har låg potential att bioackumuleras.

### Detaljerad miljöinformation

### Detailed Background Information

### Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

The PEC is calculated according to the following formula:

$$\text{PEC } (\mu\text{g/L}) = \frac{A \times 10000000000 \times (100-R)}{365 \times P \times V \times D \times 100} = 1.37 \times 10^{-6} \times A \times (100-R)$$

It is based on the following data:

A = 723.3644 kg (sales data for 2022 obtained from IQVIA)

R = 0 % removal rate (conservative estimate)

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

V (L/Day)= volume of wastewater per capita and day = 200 (ECHA default)<sup>1</sup>

D= factor for dilution of waste water by surface water flow= 10 (ECHA default)<sup>1</sup>

$$PEC = 1.37 \times 10^{-6} \times A \times (100-R)$$

$$PEC = 1.37 \times 10^{-6} \times 723.3644 \times (100-0)$$

$$PEC = 0.099 \mu\text{g/L}$$

#### **Excretion (metabolism):**

After human ingestion, apixaban and some of its metabolites are excreted in the urine and feces with unchanged apixaban accounting for approximately 57% of the ingested dose<sup>2</sup>. None of the metabolites identified were detected in amounts at or above 10% of the administered dose. No removal is used as a worst case scenario for the PEC calculation above.

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

##### ***Ecotoxicological studies***

Activated Sludge (OECD 209)<sup>3</sup>

EC<sub>50</sub> > 1000 mg/L (highest dose tested)

NOEC = 1000 mg/L

Algae (*Pseudokirchneriella subcapitata*) (OECD 201)<sup>4</sup>

EC<sub>50</sub> 72 h (growth rate/biomass) > 23 mg/L

NOEC 72 h (growth rate/biomass) = 3.6 mg/L

Crustacean (*Daphnia magna*)

##### ***Chronic Toxicity (OECD 211)***<sup>5</sup>

NOEC 21 days (survival/body length) = 23 mg/L

NOEC 21 days (reproduction) = 9.6 mg/L

Fish (Fathead Minnow; *Pimephales promelas*)

##### ***Chronic Toxicity (OECD 210)***<sup>6</sup>

NOEC 32 days/28 days post hatch (hatching success/growth/mortality) = 10 mg/L

## Environmental Risk Classification (PEC/PNEC Ratio)

The PNEC for aquatic organisms is based on the lowest NOEC of 3.6 mg/L (3600 µg/L), noted in the algae toxicity study. An assessment factor of 10 is applied to the ecotoxicity base set of three chronic studies.

$$\text{PNEC}_{\text{aquatic}} = 3600 / 10 = 360 \text{ µg/L}$$

The PEC/PNEC calculation below for the aquatic compartment is less than 0.1 which justifies the phrase "Use of apixaban has been considered to result in insignificant environmental risk"

$$\begin{aligned} \text{PEC} / \text{PNEC}_{\text{aquatic}} &= 0.099 / 360 \\ &= 2.75 \times 10^{-4} \end{aligned}$$

## Degradation

### Biotic Degradation

Ready Degradability (OECD 301B)<sup>7</sup>:

-3.88% primary degradation over 30 days; not readily biodegradable

Simulation Studies (OECD 308)<sup>8</sup>:

The fate of apixaban was studied in two natural aquatic sediment systems. The sediment from Taunton River (Sediment 1) was a fine textured loam with a slightly acidic pH and high organic carbon content (2.8% w/w dry weight), while that from the Weweantic River (Sediment 2) was a coarse textured, slightly acidic sand with a lower organic carbon content (0.47% w/w dry weight). In both aerobic sediment systems apixaban declined in the water phase over time (<15% of initial concentration at day 102) and increased in the sediment phase (71.8-75.1% of initial radioactivity after 102 days). Non-extractable radioactivity in the sediment accounted for up to 34.9% of applied radioactivity. Several peaks that were presumed to be metabolites of apixaban were noted but none reached 10% of the administered dose and were not analyzed any further. A small amount of material did degrade completely as noted by the 5.1 and 3.2% CO<sub>2</sub> evolution in the two systems. The total system half-life of apixaban (based on dissipation rates) for sediment 1 and 2 was 100 and 182 days, respectively. Total recoveries of radioactivity (mass balances) for sediments 1 and 2 were 98.3% and 99.1 % of the amounts initially applied, respectively. In both aquatic sediments, evolution of volatile radioactivity was minimal (<0.1% applied radioactivity after 100 days). Non-extractable radioactivity in sediment accounted for up 34.9 and 19.8% applied radioactivity in sediments 1 and 2, respectively. Extractions were performed using a shaker table at 150 rpm for 10 minutes with acetonitrile, acetonitrile:water (80:20 by volume) and acetonitrile:water:hydrochloric acid (80:20:0,1 % by volume). These extraction procedures were deemed to be suitable.

Based on the OECD 301B study, apixaban is not readily biodegradable. Based on the DT<sub>50</sub>s determined in the OECD 308 study and the 2012 FASS guidance for pharmaceutical companies, the phrase apixaban "is slowly degraded in the environment" is justified.

### Bioaccumulation

Partitioning Coefficient (OECD 107)<sup>9</sup>:

Log  $D_{o/w}$  = 1.20 at approximately neutral pH at 21°C (apixaban is non-ionizable)

Justification of chosen bioaccumulation phrase:

Since the Log  $D_{o/w}$  is less than 4, the phrase “apixaban has low potential for bioaccumulation” is justified.

### Soil Sorption/Desorption

Determination of the Koc Coefficient (OECD 121)<sup>10</sup>

Koc = 12.2 l/kg (purified water)

The  $K_{oc}$  value of 12.2 l/kg indicated apixaban has a low affinity to organic matter in soils and sludge and is well below the 10000 l/kg threshold; therefore, terrestrial testing was not be conducted on apixaban. The  $K_{oc}$  study for apixaban used the OECD 121 method. This was conducted before the EMA selected a preferred method<sup>11,12</sup>. The  $K_{oc}$  method used, although not a preferred method did result in a low  $K_{oc}$  value that even if conducted using a preferred method would have been unlikely to result in a largely different  $K_{oc}$  value. Considering the difference between the existing test data of 12.2 l/kg, versus the threshold value for terrestrial testing, 10000 l/kg, rerunning a  $K_{oc}$  study using a preferred method would not add value.

### PBT/vPvB Assessment

Apixaban does not meet the criteria to be considered a PBT or vPvB substance.

### References

1. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. [http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
2. Raghavan, N., D. Zhang, H. Zhang, D. Pinto, Biotransformation of [<sup>14</sup>C] BMS-562247 after Oral Administration to Humans, Bristol-Myers Squibb Pharmaceutical Research Institute, 28-Mar-2005, Document Control No. 930010261.
3. Turk, R. S., 2009, Apixaban (BMS 562247-01) - Activated Sludge Respiration Inhibition Test Following OECD Guideline 209, Springborn Smithers Laboratories, Inc., Study No. 12534.6337, Document Control No. 930040866.
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12. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010) 17 March 2011.