FASS

Eliquis

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:

$$PEC\ (\mu g/L) = \frac{A \times 1000000000 \times (100-R)}{365 \times P \times V \times D \times 100} = 1.37 \times 10^{-6} \times A \times (100-R)$$

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 inhaitants in Sweden = 10×10^6
V (L/Day)= volume of wastewater per capita and day = 200 (ECHA default)[1]
D= factor for dilution of waste water by surface water flow= 10 (ECHA default)[1]

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

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

PEC = 0.099 µg/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[2]. 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)[3]

EC_{50} > 1000 mg/L (highest dose tested)
NOEC = 1000 mg/L

Algae (*Pseudokirchneriella subcapitata*) (OECD 201)[4]

EC_{50} 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)[5]

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)[6]

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.

$PNEC_{aquatic}$ = 3600 / 10 = 360 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"

PEC/ $PNEC_{aquatic}$ = 0.099 / 360

= 2.75×10^{-4}

Degradation

Biotic Degradation

Ready Degradability (OECD 301B)[7]:

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

Simulation Studies (OECD 308)[8]:

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_2 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_{50}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)[9]:

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)[10]

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[11,12]. 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

2. Raghavan, N., D. Zhang, H. Zhang, D. Pinto, Biotransformation of [^{14}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.

4. Hoberg, J., 2008, Apixaban (BMS 562247-01) – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline 201, Springborn Smithers Laboratories, Inc., Study No. 12534.6338, Document Control No. 930032433.

5. Sayers, L. E., 2008, Apixaban (BMS 562247-01) - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Static-Renewal Conditions, Following OECD Guideline 211, Springborn Smithers Laboratories, Inc., Study No. 12534.6339, Document Control No. 930032449.

6. York, D., 2008, Apixaban (BMS 562247-01) – Early Life-Stage Toxicity Test with Fathead Minnow, (*Pimephales promelas*), Following OECD Guideline 210, Springborn Smithers Laboratories, Inc., Study No. 12534.6340, Document Control No. 930032439.

7. McLaughlin, S. P., 2008 Apixaban (BMS 562247-01) – Determination of the Biodegradability Based on OECD Method 301B (CO2 Evolution Test) Springborn Smithers Laboratories, Inc., Study No. 12534.6341, Document Control No. 930032440.

8. Turk, R., N. R. Lentz, 2009 [^{14}C]Apixaban (BMS 562247-02) - Aerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308, Springborn Smithers Laboratories, Inc., Study No. 12534.6347, Document Control No. 930040867.

9. Hatch, J. D., 2009 Determining the Partitioning Coefficient (n-Octanol/Water) of Apixaban (BMS 562247-01) by the Flask-Shaking Method Following OECD Guideline 107, Springborn Smithers Laboratories, Inc., Study No. 12534.6335, Document Control No. 930040857.

10. Hatch, J. D., 2009, Apixaban (BMS 562247-01) - Determination of the Koc Coefficient Following OECD Guideline 121 Springborn Smithers Laboratories, Inc., Study No. 12534.6336, Document Control No. 930040856.

11. Committee for Medicinal Products for Human Use (European Medicines Agency). Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), 01 June 2006.

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.