FASS

IMBRUVICA

℞ (F)

Janssen

Filmdragerad tablett 420 mg
(Gul-gröna till gröna avlånga tabletter (17,5 mm långa och 7,4 mm breda) präglade med ”ibr” på ena sidan och ”420” på andra sidan.)

Antineoplastiska medel, proteinkinashämmare

Aktiv substans:
Ibrutinib

ATC-kod:
L01EL01

Läkemedel från Janssen omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Ibrutinib

Miljörisk: Användning av ibrutinib har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Ibrutinib bryts ned långsamt i miljön.
Bioackumulering: Ibrutinib har låg potential att bioackumuleras.

Detaljerad miljöinformation

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L)	=	$(A*10^{9}*(100-R))/(365*P*V*D*100)$
		$= 1.37*10^{-6}*A*(100-R)$
PEC	=	0.005065164 µg/L
Where:		
A	=	

		36.972 kg (total sold amount API in the most recent sales data for Sweden (2020) was distributed by IQVIA in 2021)
R	=	X % removal rate (due to loss by ad sorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available.
P	=	number of inhabitants in Sweden = $10 * 10^6$
V (L/day)	=	volume of wastewater per capita and day = 200 (ECHA default) (Ref. 9)
D	=	factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Ref. 9)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae

Algal growth inhibition test with the green alga (*Pseudokirchneriella subcapitata*) (OECD 201) [Ref. 1]:
$E\gamma C_{50}$ 72 h (biomass) = 1.02 mg/L
NOECγ (biomass) = 0.0370 mg/L
E_rC_{50} 72 h (growth rate) = 4.16 mg/L
$NOEC_r$ (growth rate) = 0.129 mg/L

Crustacean

Chronic

Reproduction test with water-flea (*Daphnia magna*) (OECD 211) [Ref. 2]:
NOEC 21 days (reproduction) = 47.9 µg/L

Fish

Chronic

Fish early life stage test with fathead minnow (*Pimephales promelas*) (OECD 210) [Ref. 3]:
NOEC 28 days (mortality) = 15.5 µg/L

Other ecotoxicity data

Activated sludge respiration inhibition test (OECD 209) [Ref. 4]
EC_{50} 3h (respiration inhibition) > 1000 mg/L
NOEC 3h = 1000 mg/L

Environmental risk classification (PEC/PNEC ratio)

Calculation of Predicted No Effect Concentration (PNEC)

PNEC (µg/l) = lowest NOEC/10, where 10 is the assessment factor used. NOEC for fish 15.5 µg/L has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 15.5 µg/L/10 = 1.55 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.005065164 /1.55 = 0.003267848 i.e. PEC/PNEC ≤ 0.1

Conclusion for environmental risk:

Use of ibrutinib has been considered to result in insignificant environmental risk.

DEGRADATION

Biotic degradation

Ready biodegradation

Ibrutinib was investigated for its ready biodegradation in a 28-day manometric respirometry test according to OECD 301F [Ref. 5]:
Result: Not readily biodegradable.

Simulation study Aerobic degradation in aquatic sediment systems:

Ibrutinib was investigated for its aerobic degradation in a 100-day aquatic sediment test, according to OECD 308 [Ref. 6]:
The fate of ibrutinib has been studied in two natural aquatic sediment systems (Swiss Lake and Calwich Abbey Lake) under laboratory conditions.
In Calwich Abbey Lake aquatic sediment, the total radioactivity in the water layer declined from a mean of 90.1% of the applied radioactivity at time zero to 2.2% after 100 days. In the sediment, there was a corresponding increase in the total radioactivity to a mean of 84.1% of the applied radioactivity at 100 days. The proportion of radioactivity remaining unextracted in the sediment increased to a mean of 47.7% of the applied radioactivity after 100 days.

Dissipation of radioactivity followed a similar pattern in the Swiss Lake aquatic sediment. The total radioactivity in the water layer declined from a mean of 91.1% of the applied radioactivity at time zero to 6.3% after 100 days. In the sediment, total radioactivity increased to a mean of 79.6% of the applied radioactivity at 100 days. The proportion of radioactivity remaining unextracted in the sediment increased to a mean of 54.9% of the applied radioactivity after 100 days.

In both aquatic sediments, evolution of volatile radioactivity was minimal, up to a mean of 4.0 and 2.8% of the applied radioactivity after 100 days, from the Calwich Abbey Lake and Swiss Lake system, respectively. Non-extractable radioactivity in the Calwich Abbey Lake and Swiss Lake sediment was mainly associated with the humin fractions.

DT_{50} and DT_{90} values for the decline of ibrutinib from the water, the sediment and from the total aquatic sediment system are shown below:

	Calwich Abbey Lake		Swiss Lake	
	DT_{50} (days)	DT_{90} (days)	DT_{50} (days)	DT_{90} (days)
Water	4.2	14	9.5	32
Sediment	62	206	54	179

Total system	38	126	41	135

Used analytical methods:

- LC-MS/MS was carried out on the sediment extracts from Calwich Abbey Lake system taken at 100 days.
- HPLC was carried out with UV and radioactivity detection.
- Samples were analysed by normal phase TLC.
- The decline of Ibutinib in the water phase, sediment and total system for Calwich Abbey and Swiss Lake were modelled using the Single Firs Order (SFO) kinetic model.

Conclusion for degradation:
Ibrutinib is slowly degraded in the environment.

BIOACCUMULATION
Partition coefficient octanol/water
The partition coefficient octanol/water was determined using the shake flask method (OECD 107). [Ref. 7]
The log Kow was determined at pH 4.0, 7.0 and 9.0. Log K_{ow} = 3.8 (pH 4.0)

Log K_{ow} = 4.0 (pH 7.0)

Log K_{ow} = 4.0 (pH 9.0)

Bioconcentration
The bioconcentration and depuration characteristics of ibrutinib in the rainbow trout in a flow through system were examined according to OECD 305 [Ref. 8].

$BCF_{low\ dose}$ = 13.5
$BCF_{high\ dose}$ = 68.0
Ibrutinib is not expected to bioaccumulate in fish.

Conclusion for bioaccumulation:
Ibrutinib has low potential for bioaccumulation.

Excretion (metabolism)

No data available.

PBT/vPvB assessment

	PBT-criteria	Results for ibrutinib
P	DT_{50} freshwater > 40 days or DT_{50} sediment > 120 days	DT_{50} freshwater = 4.6 – 9.5 days DT_{50} total system = 38 - 41 days
B	BCF > 2000	BCF = 68.0 (high dose) BCF = 13.5 (low dose)
T	Chronic NOEC < 10 µg/L or CMR or endocrine disrupting	$NOEC_{algae}$ = 4.16 mg/L $NOEC_{daphnia}$ = 47.9 µg/L $NOEC_{fish}$ = 15.5 µg/L

None of the PBT-criteria are fulfilled. Therefore, ibrutinib is not considered a PBT-substance.

References

1. J. Davies; Ibrutinib – Algal growth inhibition assay; HLS Study IMB0022; Janssen Study Number RMD1178; October 16, 2013.
2. J. Davies; Ibrutinib – Daphnia magna reproduction toxicity test; HLS Study IMB0023; Janssen Study Number RMD1179; February 28, 2014.
3. R. Allen; Ibrutinib – Fish early life stage test; HLS Study IMB0024; Janssen Study Number RMD1180; March 31, 2014.
4. R.A. Dickinson; Ibrutinib – Activated sludge respiration inhibition test; HLS Study IMB0021; Janssen Study Number RMD1177; April 24, 2013.
5. R.A. Dickinson; Ibrutinib – Assessment of ready biodegradability of respirometry; HLS Study IMB0020; Janssen Study Number RMD1176; April 24, 2013.
6. E. Dodd; Ibrutinib – Aerobic degradation in aquatic sediment systems; HLS Study IMB0025; Janssen Study Number 1181; January 03, 2014.
7. P. Sydney; Ibrutinib – Partition coefficient; HLS Study IMB0018; Janssen Study Number RMD1174; March 27, 2013.
8. T. Kane; Ibrutinib – Bioconcentration in rainbow trout; HLS Study IMB0075; Janssen Study Number RMD1188; March 6, 2014.
9. 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