FASS

Ticagrelor Reddy

M

Betapharm Arzneimittel

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Filmdragerad tablett 60 mg

(Tillhandahålls ej) (Runda, bikonvexa, vita till benvita filmdragerade tabletter med en diameter på ca. 8 mm och märkta med ’T’ på den ena sidan och omärkta på den andra.)

Trombocytaggregationshämmande medel, exklusive heparin

Aktiv substans:

Tikagrelor

ATC-kod:

B01AC24

Läkemedel från Betapharm Arzneimittel omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för ticagrelor är framtagen av företaget AstraZeneca för Brilique, POSSIA

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

Nedbrytning: Ticagrelor bryts ned i miljön.
Bioackumulering: Ticagrelor har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 0.090 µg/L / 53 µg/L = 0.00170
PEC/PNEC ≤ 0.1

Environmental Risk Classification
Predicted Environmental Concentration (PEC)

The PEC is based on the following calculation:

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

PEC (µg/L) = $1.37*10^{-6}*A*(100-R)$

PEC = $1.37 * 10^{-6} *588.20*(100-0)$

= 0.090 µg/L

Where;
A (kg/year) = total sold amount API in Sweden year 2020, data from IQVIA
= 588.20 kg

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)
= 0%

P = number of inhabitants in Sweden
$=10*10^6$

V (L/day) = volume of wastewater per capita and day
= 200 L/day (Ref 1)

D = factor for dilution of waste water by surface water flow
= 10 (Ref 1)
Note: The factor 10^9 converts the quantity used from kg to µg

Metabolism and excretion

Ticagrelor is extensively metabolised in humans with approximately 27% of the dose
excreted as the parent compound.

Ecotoxicity Data

Study Type	Method	Result	Reference
Activated sludge, respiration inhibition test	OECD 209	3 h NOEC = 100 mg/L 3 h EC_{50} >100 mg/L	2
Toxicity to the freshwater green alga, *Selenastrum capricornutum*	OECD 201	72 h $NOEC_{growth\ rate}$ = 0.82 mg/L 72 h $LOEC_{growth\ rate}$ = 1.9 mg/L	3

		72 h $EC50_{growth\ rate}$ = >5.2 mg/L 72 h $NOEC_{biomass}$ = 0.82 mg/L 72 h $LOEC_{biomass}$ = 1.9 mg/L 72 h $EC50_{biomass}$ = >5.2 mg/L	
Acute toxicity to *Daphnia magna*	OECD202	48 h EC50 (immobility) = 1.4 mg/L	4
Acute toxicity to rainbow trout, *Oncorhynchus mykiss*	OECD203	96h LC50 (mortality) >2.7 mg/L	5
Chronic toxicity to *Daphnia magna*	OECD 211	21 d NOEC (reproduction, survival length) = 0.53 mg/L 21 d LOEC (reproduction, survival length) = 1.7 mg/L	6
Fish early-life stage toxicity with fathead	OECD 210	32 d NOEC (hatch, survival, length and	7

minnow, *Pimephales promelas* (note 2)		weight) = 1.8 mg/L 32 d LOEC (hatch, survival, length and weight) >1.8 mg/L	
Toxicity to sediment dwelling midge, *Chironomus riparius*	OECD 218	28 d NOEC (development rate, total emergence, sex ratio) = 30 mg/kg dry weight 28 d LOEC (development rate, total emergence, sex ratio) > 30 mg/kg dry weight	8

Predicted No Effect Concentration (PNEC)

Long-term tests have been undertaken for species from three trophic levels. Therefore, the PNEC is based on the chronic toxicity to the giant water flea (*Daphnia magna),* 0.53 mg/L, and an assessment factor of 10 is applied, in accordance with ECHA guidance.

PNEC = 530/10 µg/L = 53 µg/L

Environmental Risk Classification (PEC/PNEC ratio)

PEC/PNEC = 0.090 µg/L / 53 µg/L = 0.00170
PEC/PNEC = ≤ 0.1

The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase, and the risk phrase for PEC/PNEC = ≤ 0.1 reads as follows; “Use of ticagrelor has been considered to result in insignificant environmental risk” has been assigned.

In Swedish: “Användning av Tikagrelor har bedömts medföra försumbar risk för miljöpåverkan” under the heading Miljörisk.

Environmental Fate Data

Study Type	Method	Result	Reference
Aerobic biodegradation	OECD 301F	<5% degradation after 28 days Not readily biodegradable	9
Adsorption/desorption to sludge	OPPTS 835.1110	$K_{d(ads)}$ = 1571 K_{oc} = 4246	10
Aerobic transformation in aquatic sediment systems	OECD 308	• High organic carbon system	11

		DT_{50} total system = 11.3 days with <15% of applied radioactivity remaining as parent compound (2.3% in water + 8.0% in sediment) compound at the end of the study • Low organic carbon system DT_{50} total system = 19.6 days with <15% of applied radioactivity remaining as parent compound (0% in water + 2.8%	

		in sediment) at the end of the study Evidence suggest that the substance is degraded and will not be persi stent in the aquatic environment	

Results from the aerobic biodegradation test (Ref. 9), showed that ticagrelor is not readily biodegradable.

Evidence from the OECD 308 study (Ref. 11) indicates that ticagrelor is likely to dissipate from the aqueous phase and partition into the sediment phase.

High organic matter (HOM) sediment system:

The average mass balances upon application (day zero) showed 22% and 29% of the applied radioactivity remained unaccounted for in the high and low organic matter vessels, respectively. Recoveries in all vessels sacrificed after day 0 were showed mass balances ranging 81.8 to 105.8% of applied radioactivity (AR) throughout the 99-day study.

The radiolabelled ticagrelor dissipated rapidly from the water phase, with a half-life of 2.2 days. The proportion of ticagrelor remaining in the water phase at the end of the study was 6.1% AR in the high organic matter system while no remaining ticagrelor

was observed in the water phase of the low organic matter system at the end of the study.

Sediments were extracted with ethanol initially and additional solvent extractions performed to address the high proportion of unextracted residue (observed particularly in the high organic matter sediment). The additional solvent extractions removed varying amounts of additional radioactivity; from the high organic matter sediment, THF, DMSO and SolueneTM removed 17, 18 and 19% AR, respectively and from low organic matter sediment methanol, acetone, THF, DMSO and SolueneTM all removed a further 2 to 8% AR. Nonetheless, at the end of the study an average of 51.7% AR and 31.75% AR were bound to the high and low organic matter sediments, respectively.

The proportion of radiolabel extracted from the sediment and identified as ticagrelor decreased from a maximum of 32.9% at day 14 to 8.0% AR by day 99 in the high organic matter sediment and from a maximum of 47.69% at day 14 to 2.8% AR by day 99 in the low organic matter sediment.
A significant proportion of ticagrelor was mineralised in both systems in this study, with 14% AR and 29% AR having been evolved as carbon dioxide in the high and low organic matter systems at the end of the study.
The calculated total system half-lives were 11.3 days and 19.6 days for the high and low
organic matter systems.

Based on the data above, ticagrelor is not predicted to be readily biodegraded during wastewater treatment. However, there is evidence that metformin hydrochloride will degrade within the aquatic environment.

Based on the above information, the phrase “Ticagrelor is degraded in the environment.” has been assigned.

In Swedish: “Tikagrelor bryts ned i miljön.”under the heading “Nedbrytning”.

Physical Chemistry Data for Ticagrelor

Study Type	Method	Result	Reference
Preliminary hydrolysis	OECD 111	18% after 5 days at 50°C (pH 5) <10% after 5 days at 50°C (pH 7) <10% after 5 days at 50°C (pH9) Hydrolysis half-life at 25°C ≥ 1 year	12
Water solubility	OECD 105	5.3 mg/L at pH 5 3.5 mg/L at pH 7 11 mg/L at pH 9	13

Octanol/water partition coefficient	OECD 107	log D_{ow} > 4.02 at pH 5, 7 and 9	14

Ticagrelor is not ionisable, is water soluble and hydrolytically stable. It is not readily biodegradable during sewage treatment and is not predicted to significantly partition onto sludge solids. In the natural environment, ticagrelor is expected to partition into aquatic sediments and undergo significant degradation. The risk of bioaccumulation of ticagrelor in aquatic organisms is low.

Therefore, the phrase “Ticagrelor is degraded in the environment” has been assigned.

In Swedish: “Tikagrelor bryts ned i miljön” under the heading ‘Nedbrytning’.

Bioaccumulation Data

Study Type	Method	Result	Reference
Preliminary study: bioconcentration potential in rainbow trout (*O. mykiss*)	OECD305	BCF at 1.0 µg/L = 6.36 L/Kg (based on total radioactivity) Not bioaccumulative	15

Ticagrelor is not ionisable, however, the octanol-water distribution coefficient, LogDow, was determined across an environmentally relevant pH-range (Ref. 14).

Bioconcentration of ticagrelor in *Oncorhynchus mykiss* was assessed, and the whole body BCF at 1.0 µg/L of ticagrelor was 6.36 after 28 days uptake. Since the BCF is < 500, ticagrelor has a low potential for bioaccumulation. Therefore, the phrase ‘Ticagrelor has low potential for bioaccumulation’ has been assigned.

In Swedish: ”Tikagrelor har låg potential att bioackumuleras,” under the heading ”Bioackumulering”.

References

1. [ECHA] European Chemicals Agency. 2008. Guidance on Information Requirements and Chemical Safety Assessment.
2. AZD1640: Effect on the respiration rate of activated sludge. Brixham Environmental Laboratory, UK. Report No BL8213. December 2005.
3. AZD6140: Toxicity to the green alga Selenastrum capricornutum. Brixham Environmental Laboratory, UK. Report No BL8237. December 2006.
4. AZD1640: Acute Toxicity to Daphnia Magna. Brixham Environmental Laboratory, UK. Report No BLS3310. October 2005.
5. AZD1640: Acute Toxicity to rainbow trout (Oncorhynchus mykiss).
   Brixham Environmental Laboratory, UK. Report No BLS3359. October 2005.

6. AZD1640: Chronic Toxicity to Daphnia Magna. Brixham Environmental Laboratory, UK. Report No BL8604. September 2008.
7. AZD1640: Determination of effects on the early-life stage of the fathead minnow (Pimephales promelas). Brixham Environmental Laboratory, UK. Report No BL8362. July 2007
8. [^{14}C]AZD1640: Effects in sediment on emergence of the midge, Chironomus riparius. Brixham Environmental Laboratory, UK. Report No BL8659. February 2009.
9. AZD1640: Determination of 28 day ready biodegradability. Brixham Environmental Laboratory, UK. Report No BL8262. March 2006.
10. AZD1640: Adsorption and desorption of sewage sludge. Brixham Environmental Laboratory, UK. Report No BL8344. December 2006.
11. AZD1640: Aerobic transformation in aquatic sediment. Brixham Environmental Laboratory, UK. Report No BL8610. December 2008.
12. AZD1640: Hydrolysis as a function of pH – preliminary study results summary. Brixham Environmental Laboratory, UK. Report No BLS3343. July 2006.
13. AZD1640: Water solubility. Brixham Environmental Laboratory, UK. Report No BL8220. December 2005.
14. ADZ1640: Determintation of n-octanol-water partition coefficient. Brixham Environmental Laboratory, UK. Report No BL8280. January 2007.
15. [^{14}C]AZD1640: Determination of the accumulation of [14C]AZD1640 in rainbow trout (Oncorhynchus mykiss). Brixham Environmental Laboratory, UK. Report No BL8680. September 2008.