

Quetiapine Accord

M R F

Accord Healthcare AB

Depottablett 50 mg

(persikofärgade, bikonvexa, filmdragerade tabletter, släta på ena sidan och präglade med "Q50" på den andra, 11,2 x 11,2 mm)

Neuroleptika; diazepiner, oxazepiner och tiazepiner

Aktiv substans:

Kvetiapin

ATC-kod:

N05AH04

Läkemedel från Accord Healthcare AB omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för kvetiapin är framtagen av företaget AstraZeneca för Seroquel, Seroquel®

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

Nedbrytning: Quetiapin bryts ned långsamt i miljön.

Bioackumulering: Quetiapin har låg potential att bioackumuleras.

Detaljerad miljöinformation

$PEC/PNEC = 0.33 \mu\text{g/L} / 10.0 \mu\text{g/L} = 0.033$

$PEC/PNEC \leq 0.1$

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

The PEC is based on following data:

$PEC (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100)$

$PEC (\mu\text{g/L}) = 1.37 \cdot 10^{-6} \cdot A \cdot (100 - R)$

$PEC = 1.37 \cdot 10^{-6} \cdot 2430.60 \cdot (100 - 0)$

$= 0.33 \mu\text{g/L}$

A (kg/year) = total sold amount API in Sweden year 2021, data from IQVIA/Lif
= 2430.60 kg/year

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

P = number of inhabitants in Sweden = 10×10^6

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default)

Note: The factor 10^9 converts the quantity used from kg to μg .

Metabolism

After oral administration, quetiapine is eliminated almost completely by metabolism, as < 1% of the dose is excreted with urine and faeces as unaltered parent. Approximately 73% of the dose is excreted as metabolites in urine and 21% is excreted in faeces. (Ref. 1)

Ecotoxicity data

Study	Method	Result	Reference
Toxicity to Cyanobacterium (Blue-Green Alga) <i>Microcystis aeruginosa</i>	US FDA Technical Assistance Document 4.01	21d NOEC _{growth} 32mg/L 21d LOEC _{growth} 64mg/L 21d NOEC _{cell density} 4.0mg/L 21d LOEC _{cell density} 8.0mg/L	2
Toxicity to Green Alga <i>Pseudokirchneriella subcapitata</i> (formerly known as <i>Selenastrum capricornutum</i>)	US FDA Technical Assistance Document 4.01	14d NOEC _{growth} = 2.5mg/L 14d LOEC _{growth} = 5.0mg/L 14d NOEC _{cell density} = 2.5mg/L 14d LOEC _{cell density} = 5.0mg/L	3
Chronic toxicity to <i>Daphnia magna</i>	US FDA Technical Assistance Document 4.09	21d LC50 > 32mg/L 21d NOEC = 18mg/L 21d LOEC = 32mg/L	4
Chronic toxicity to Midge <i>Chironomus riparius</i>	OECD 218	28d EC50 _{emergence} 465 mg/kg dry sediment 28d NOEC _{emergence} 125 mg/kg dry sediment 28d LOEC _{emergence} 250 mg/kg dry sediment	5
Acute toxicity to			

Study	Method	Result	Reference
Bluegill Sunfish <i>Lepomis macrochirus</i>	US FDA Technical Assistance Document 4.11	96 h LC50 = 19.3mg/L 96 h NOEC = 1.8mg/L	6
Acute toxicity to Rainbow Trout <i>Oncorhynchus mykiss</i>	US FDA Technical Assistance Document 4.11	96 h LC50 = 22.0mg/L 96 h NOEC = 1.0mg/L	7
Early-life stage toxicity to Fathead Minnow <i>Pimephales promelas</i>	OECD 210	32 d NOEC = 0.1mg/L* 32 d LOEC = 0.32mg/L*	8
Activated sludge, respiration inhibition test	OECD209	3 hour EC50 >100mg/L 3 hour NOEC = 100mg/L	9

*The relevant effects measured were hatch, survival, length, wet and dry weight.

PNEC (Predicted No Effect Concentration)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the results from the chronic toxicity to fathead minnow (*Pimephales promelas*), the most sensitive species, and an assessment factor of 10 is applied, in accordance with ECHA guidance (ref. 10).

$$\text{PNEC} = 100 \mu\text{g/L} / 10 = 10 \mu\text{g/L}$$

Environmental risk classification (PEC/PNEC ratio)

$$\text{PEC/PNEC} = 0.33 \mu\text{g/L} / 10.0 \mu\text{g/L} = 0.033$$

PEC/PNEC ≤ 0.1 which justifies the phrase: "Use of Quetiapine has been considered to result in insignificant environmental risk."

In Swedish: "Användning av Quetiapin har bedömts medföra försumbar risk".

Environmental Fate Data

Study	Method	Result	Reference
Ready biodegradability: Manometric respirometry	OECD 301F	28d Biochemical oxygen demand (BOD ₂₈) = 0% 28d carbon loss= 10 % 28d test substance loss = 24% Not readily biodegradable	11
Anaerobic biodegradability	UK DoE Modified According to ISO/CD 11734	0 % biodegradation 52% compound removal by day 57 in anaerobic sludge	12
Aerobic transformation in aquatic sediment systems	OECD 308	HOM DT ₅₀ (water) = 5.2d LOM DT ₅₀ (water) = 18d HOM = 14.0% parent compound remaining at Day 101	13

Study	Method	Result	Reference
		LOM < 10% parent compound remaining at Day 101	
Percentage Hydrolysis / Hydrolysis Half-life	US FDA Technical Assistance Document 3.09	Hydrolysis at 50°C (at pH 5, 7 and 9, respectively) was <10% after 5 days. Estimated $DT_{50} \geq 1$ yr @ 25°C	14
Adsorption and desorption to sewage sludge	OPPTS 835.1110	$K_d(ads) = 335$ $K_d(des) = 247 - 471$ K = 905 L/Kg*	15
Soil adsorption and desorption	US FDA Technical Assistance Document 3.08	<ul style="list-style-type: none"> • Nebo (pH 4.9, OC 1.6%); $K_d = 3600$ L/Kg ($K_{oc} = 220,000$ L/Kg) • East Jubilee (pH 5.8, OC 2.2%); $K_d = 180$ L/Kg ($K_{oc} = 8,000$ L/Kg) • Kenny Hill (pH 7.7, OC 3.1%); $K_d = 45$ L/Kg ($K_{oc} = 1,400$ L/Kg) 	16

*Calculated $K_{oc} = K_{d(ads)} / 0.37$ (ref. 17)

Degradation

Aerobic biodegradation

A ready biodegradation test of quetiapine fumarate was undertaken by using aerobic microorganisms from a sewage treatment works to investigate their potential to readily degrade the substance. The test ended after 28 days. The results showed that quetiapine fumarate is not readily biodegradable.

Aerobic transformation in aquatic sediment systems

The degradation of quetiapine fumarate in aquatic sediment systems was assessed according to the OECD 308 Test Guideline. Two different sediments were used, one with high organic matter (HOM) and one with low organic matter (LOM) content over the 101 day test period.

In both, the high and low organic matter test vessels, quetiapine fumarate rapidly dissipated from the water phase and there was no evidence of mineralisation. In HOM sediment there was evidence to show that quetiapine fumarate was degraded, but there was insufficient analytical data to quantify the rate. The LOM sediment showed no evidence of quetiapine present. At the end of the study, <15% parent compound was reported to remain in the HOM system, with 14% remaining in the sediment phase and any remaining in the water phase being below the limit of quantification (LOQ) of 10%. The study reported no parent compound remaining in the LOM total system, indicating any parent compound residue was below the LOQ.

Based on the data available, the study passes the criteria for 'the substance is degraded in the environment' (DT_{50} of both systems is ≤ 32 days and <15% parent remaining at the end of the study).

However, the whole system DT50s are not reported due to issues with the analytical method and the 101-day data point for the water phase in the HOM system is missing (and 1% or more of parent compound remaining in this sample would take the total amount of parent remaining above 15% for the HOM system). It is therefore considered appropriate to conservatively conclude that: 'Quetiapine is slowly degraded in the environment'.

In Swedish: 'Quetiapin bryts ned långsamt i miljön'.

Physical Chemistry Data

Study	Method	Result	Reference
Solubility water	US FDA Technical Assistance Handbook 3.01	16 d @ pH 5 =10800 mg/L 20 d @ pH 7 =1600 mg/L 6 d @ pH 9 =360 mg/L	18
Solubility water	-	3.29mg/mL	19
Dissociation Constant	-	pKa = 6.83 in phosphate buffer at 22C pKa = 3.32 in formic buffer at 22C	
Octanol-Water Partition Coefficient	FDA Technical Assistance Handbook 3.02	LogP = 0.5	20
Partition coefficient		LogDow = 1.4 @ pH 5 LogDow = 2.7 @ pH 7 LogDow = 2.6 @ pH 9	

Bioaccumulation

In the absence of a measured BCF value, since $\text{LogD}_{\text{ow}} < 4$ at pH 7 the substance has been assigned the phrase: 'Quetiapin has low potential for bioaccumulation'.

In Swedish: "Quetiapin har låg potential att bioackumuleras".

References

1. Investigator's Brochure Seroquel (Quetiapine fumarate; D1441000000) AstraZeneca. 13th edition, June 2008.
2. Seroquel: Toxicity to the blue-green alga *Microcystis aeruginosa*. BL5018/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
3. Seroquel: Toxicity to the green alga *Selenastrum capricornutum*. BL5017/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
4. Seroquel: Chronic toxicity to *Daphnia magna*. BL5232/B. Brixham Environmental Laboratory, Brixham, UK. September 1994.
5. Quetiapine fumarate Toxicity to the sediment-dwelling phase of the midge *Chironomus riparius*. Report No. VKS0391/073509. Sponsors reference number: 06-0052/A. Huntingdon Life Sciences Ltd. UK. December 2007.
6. Seroquel: Acute toxicity to bluegill sunfish (*Lepomis macrochirus*). BL5085/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
7. Seroquel: Acute toxicity to rainbow trout (*Oncorhynchus mykiss*). BL5084/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

8. Quetiapine fumarate: Determination of effects on the early-life stage of the fathead minnow (*Pimephales promelas*). BL8351/B. Brixham Environmental Laboratory, Brixham, UK. August 2006.
9. Quetiapine fumarate: Effect on the respiration rate of activated sludge. Report No. BL8333/B. Brixham Environmental Laboratory, Brixham, UK. June 2006.
10. Guidance on information requirements and chemical safety assessment. Chapter R.10: Characterisation of dose [concentration]-response for environment. European Chemicals Agency, 2008
11. Seroquel: Determination of 28 day ready biodegradability. Report No. BL5078/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
12. Seroquel: Determination of anaerobic biodegradability. Report No. BL5077/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
13. Quetiapine fumarate: Aerobic transformation in aquatic sediment systems. BL8364/B. Brixham Environmental Laboratory, Brixham, UK. August 2007.
14. Data generated in the US to support the environmental assessment report for ICI 204,636. Pharmaceutical research & development Report no. SP2900/B. BD4185 Zeneca Pharmaceuticals Group, Wilmington, USA. 29 March 1995.
15. Quetiapine fumarate: Adsorption and desorption to sewage sludge. Report No. BL8343/B. Brixham Environmental Laboratory, Brixham, UK. August 2006.
16. Seroquel: Soil sorption and adsorption. Report no. BL5062/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.
17. EUSES - European Union System for the Evaluation of Substances 2.1 background report - Model Calculations. 2019.
18. ICI 204,636 solubility measurements in partial fulfillment of FDA environmental-assessment requirements. Pharmaceutical research & development report no. SP3010/B. BD4118. Zeneca Pharmaceuticals, Wilmington, USA. 22 September 1995.
19. S.1.3 General Properties, Quetiapine fumarate, ZD5077. Report no. BD4184
20. ICI 204,636 log partition coefficient measurements in partial fulfillment of FDA environmental assessment requirements. Pharmaceutical research & development Report No. SP3011/B. BD4119. Zeneca Pharmaceuticals, Wilmington, USA. 3 October 1995.