FASS

Dinterom

M

Sandoz AS

Inhalationspulver, avdelad dos 320 mikrogram/9 mikrogram/dos

Avregistreringsdatum: 2022-06-21 (Tillhandahålls ej)

Aktiva substanser (i bokstavsordning):

Budesonid

Formoterol

ATC-kod:

R03AK07

För information om det avregistrerade läkemedlet omfattas av Läkemedelsförsäkringen, kontakta Läkemedelsförsäkringen.

Läs mer om avregistrerade läkemedel

Miljöpåverkan

Miljöinformationen för budesonid är framtagen av företaget AstraZeneca för Budfor, Edoflo, Eltren, Eltren forte, Eltren mite, Gardette, Gardette forte, Gardette mite, Pulmicort®, Pulmicort® Turbuhaler®, Rhinocort® Turbuhaler®, Riltrava Aerosphere,

Symbicort, Symbicort® Turbuhaler®, Symbicort® forte Turbuhaler®, Symbicort® mite Turbuhaler®, Trixeo Aerosphere

Miljörisk: Användning av budesonid har bedömts medföra låg risk för miljöpåverkan.
Nedbrytning: Budesonid bryts ned i miljön.
Bioackumulering: Budesonid har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 0.00904 µg/L / 0.09 µg/L = 0.1004

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is based on the following data and calculated using the equation outlined in the fass.se guidance (Ref 1):

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100)$
PEC (µg/L) = $1.37*10^{-6}*A*(100-R)$
PEC = $1.37* 10^{-6} * 65.9603* (100-0)$
= 0.00904µg/L

A (Kg/year) = total sold amount API in Sweden year 2023, data from IQVIA/Lif.
= 65.9603 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 = $10*10^6$ (default, Ref 1)

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

D = factor for dilution of waste water by surface water flow = 10 (default, Ref 1)

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

Metabolism and excretion

After oral inhalation budesonide undergoes an extensive degree (>90%) of biotransformation to metabolites of low corticosteroid activity on first passage through the liver. The activity of the major metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of the parent compound. The plasma elimination half-life is approximately 4 hours. Unchanged budesonide has not been detected in urine (Ref 2). However the PEC does not take into consideration metabolism and therefore provides a worst-case exposure senario.

Ecotoxicity Data

Study Type	Method	Result	Reference
Activated sludge, respiration inhibition test	OECD 209	3 hour EC50 >1000 mg/L 3 hour NOEC = 1000 mg/L	3
	OECD 201		4

Study Type	Method	Result	Reference
Toxicity to green algae, *Selenastrum capricornutum* growth inhibition test		72 hour $NOEC_{(growth\ rate)}$ = 5.6 mg/L 72 hour $LOEC_{(growth\ rate)}$ = 8.6 mg/L 72 hour $EC50_{(growth\ rate)}$ > 8.6 mg/L 72 hour $NOEC_{(biomass)}$ = 5.6 mg/L 72 hour $LOEC_{(biomass)}$ = 8.6 mg/L 72 hour $EC50_{(biomass)}$ > 8.6 mg/L	
Growth inhibition study *Pseudokirchneriella subcapitata (previously Selenastrum capricornutum)*	OECD 201	72 hour $NOEC_{(growth\ rate)}$ = 7.9 mg/L 72 hour $LOEC_{(growth\ rate)}$ > 7.9 mg/L	5

Study Type	Method	Result	Reference
		72 hour $EC50_{(growth\ rate)}$ > 7.9 mg/L 72 hour $NOEC_{(biomass)}$ = 7.9 mg/L 72 hour $LOEC_{(biomass)}$ > 7.9 mg/L 72 hour $EC50_{(biomass)}$ > 7.9 mg/L	
Daphnia magna reproduction test under semi-static conditions	OECD 211	21 day NOEC = 3.36mg/L 21 day LOEC = 6.95mg/L	6
Acute toxicity to the giant water flea, *Daphnia magna*	OECD 202	48 hour $EC50_{(immobility)}$ >14 mg/L 48 hour $NOEC_{(immobility)}$ = 3.8mg/L	7
Acute toxicity to Rainbow Trout,	OECD 203		8

Study Type	Method	Result	Reference
Oncorhynchus mykiss		96 hour LC50 (mortality) > 13 mg/L 96 hour NOEC (mortalitiy) = 13mg/L	
Life-cycle toxicity test with the Zebrafish, *Danio rerio*	OECD review paper on fish lifecycle tests / OPPTS 850.1500	180/181 day NOEC(Male wet weight and length; F0 larval survival) = 0.9µg/L 180/181 day LOEC(Male wet weight and length; F0 larval survival) = 2.8µg/L	9
Toxicity to sediment dwelling midge, *Chironomus riparius*	OECD 218	28 day NOEC(development/emergence) = 890 mg/Kg (sediment dry weight) 28 day LOEC(development/emergence) > 890 mg/Kg	10

Study Type	Method	Result	Reference
		(sediment dry weight)	

NOEC No Observed Effect Concentration
LOEC Lowest Observed Effect Concentration
EC50 the concentration of the test substance that results in a 50% effect
LC50 the concentration of the test substance that results in a 50% mortality

PNEC (Predicted No Effect Concentration)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. The PNEC is based on the chronic toxicity to Zebrafish (*Danio rerio*), the most sensitive species, and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 11).

PNEC = 0.9 µg/L /10 = 0.09 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.00904 µg/L / 0.09 µg/L = 0.1004

This justifies the use of:
Use of budesonide has been considered to result in low environmental risk.
In Swedish: Användning av budesonid har bedömts medföra låg risk för miljöpåverkan.

Environmental Fate Data

Study Type	Method	Result	Reference
Determination of ready biodegradability	OECD301F	Mean degradation after 28 days = 2.2 % Not readily biodegradable	12
Adsorption/desorption to sediments, soils and sludge	OECD106	Mean ± SD Kd (ads) (5 soils) = 34.6 ± 16.6 Mean ± SD Koc (ads) (5 soils) = 1629 ± 1734	13
Aerobic transformation in aquatic sediment systems	OECD308	HOM DT_{50} (water) = 6.9 days LOM DT_{50} (water) = 6.45 days HOM DT_{50} (total system) = 18.1 days* LOM DT_{50} (total system) = 12.5 days HOM $_{14}CO_2$ (98 DAT) = 54.8% AR LOM $_{14}CO_2$ (98 DAT) = 86.2% AR	14

Study Type	Method	Result	Reference
		<15% of applied radioactivity remaining as parent compound (0% in water + 3.8%* in sediment) at the end of the study	

* Results calculated for the sum of [4-14C]budesonide and M23 as [4-14C]budesonide could not be sufficiently separated from its metabolite M23 by the HPLC method employed.

Degradation

The aerobic biodegradation of budesonide was assessed according to the OECD 301F Test. Results of this test indicates that budesonide is not readily biodegradable.

The adsorption and desorption of budesonide to five soils of differing characteristics was assessed in accordance with the OECD 106 Test Guideline. The reported Kd values ranged from 20 to 66 L/kg, with a derived mean of 34.6 L/kg. The corresponding Koc values were reported as ranging from 394 to 5049 L/kg with a derived mean of 1629 L/kg. Based on these results, budesonide is not expected to partition significantly to sludge solids during sewage treatment processes.

The degradation of budesonide in aquatic sediment systems was investigated according to the OECD 308 Test Guideline.The degradation of radiolabeled budesonide was investigated in a low organic matter (LOM) content (river) versus a high organic matter (HOM) content (pond) water-sediment system under both, aerobic and anaerobic conditions, over a 98-day testing period. Only the results for the aerobic test vessels are discussed here. The test item was applied to the water layer and, at day 0, 94.3% and 91.5% of applied radioactivity (AR) were present in the water of the LOM and HOM vessels, respectively. The amount of radiolabel in the water layer decreased to 7.8% AR (LOM) and 9.6% AR (HOM) at 98 days after treatment (DAT).

The amount of radioactivity associated with the sediment phase peaked at 30 DAT (49% AR in LOM, 69% in HOM) and subsequently decreased to 19% AR in LOM and 37% AR in HOM by the end of the study. The amount of budesonide parent remaining in the total system test was 1.9% (in LOM). In the HOM pond system, budesonide could not be sufficiently separated from metabolite M23, and therefore could not be quantified separately. At 98 DAT the amount of budesonide + M23 was 3.8% AR. The study showed significant mineralization, with cumulative $^{14}CO_2$ accounting for 86.2% AR and 54.8% AR in the LOM and HOM systems, respectively. All mass balances were acceptable.

Four major metabolites (>10% AR) were found in all systems (water and sediment in both river and pond systems) as either major or minor metabolites. These were identified by mass spectrometry. The total system degradation half-life of budesonide in the LOM (river) system was 12.5 days. In the HOM (pond) system, due to poor chromatographic separation, the degradation

half-life of budesonide was calculated from the sum of budesonide and M23 and a conservative total system DT_{50} of 18.1 days was derived.

As the highest DT_{50} values reported passes the criteria of $DT_{50} \leq 32d$ for the total system, and less than 15% budesonide was remaining as the parent compound at the end of the study the following phrase is therefore assigned:
Budesonide is degraded in the environment
In Swedish: Budesonide bryts ned i miljön.

Physical Chemistry Data

Study Type	Method	Result	Reference
Solubility Water	Unknown	14 mg/L at 25^{o}C	15
Octanol-Water Partition Coefficient	OECD107	Log Pow = 3.45	16

Budesonide is not ionisable within the environmentally relevant pH range. The Log octanol-water partition coefficient is 3.45, measured at pH 7.19. Since Log P < 4, budesonide has low potential to bioaccumulate and the phrase: “Budesonide has low potential for bioaccumulation” is assigned.
In Swedish: Budesonid har låg potential att bioackumuleras.

Bioaccumulation Data

Study Type	Method	Result	Reference
Bioaccumulation in tissues of	OECD305	BCF_{L} at 3µg/L = 9 ± 3	17

carp, *Cyprinus carpio*		Not bioaccumulative in fish	

A fish bioconcentration study was conducted in carp, *Cyprinus carpio,* according to the OECD 305 Test Guideline. During the uptake phase, fish were exposed at nominal concentrations of 0.3 and 3.0 µg/L for 28 days. A steady state concentration was reached for both test concentrations after 3 days of exposure. The whole body bioconcentration factor at steady state (BCFss) was normalised for the lipid content and reported as 8 ± 3 at 0.3 µg/L and 9 ± 3 at 3.0 µg/L of budesonide. In the absence of any significant uptake, a depuration period was not required.

As a BCF < 500 was determined, the phrase:
“Budesonide has low potential for bioaccumulation” is assigned.
In Swedish: Budesonid har låg potential att bioackumuleras.

References

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16. Budesonide: Determination of the partition coefficient (n-octanol/water). Simona Nichetti. ChemService S.r.l. Controlli e Ricerche Report 169/2013. June 2013.
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Miljöinformationen för formoterol är framtagen av företaget AstraZeneca för Bevespi Aerosphere, Budfor, Edoflo, Eltren, Eltren forte, Eltren mite, Gardette, Gardette forte, Gardette mite, Oxis® Turbuhaler®, Riltrava Aerosphere, Symbicort, Symbicort® Turbuhaler®, Symbicort® forte Turbuhaler®, Symbicort® mite Turbuhaler®, Trixeo Aerosphere

Miljörisk: Användning av formoterol har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Formoterol är potentiellt persistent.
Bioackumulering: Formoterol har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 0.000050 µg/L /94 µg/L = $0.5*10^{-7}$
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 = $1.37 * 10^{-6} *0.34*(100-0)$
= 0.000050 µg/L

Where;
A (kg/year) = total sold amount API in Sweden year 2020, data from IQVIA
= 0.34 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

The major part of the dose of formoterol fumarate dihydrate is eliminated via metabolism. After inhalation, 8-13% of the delivered dose is excreted unmetabolised in the urine. (Ref 2).

Ecotoxicity Data

Study Type	Method	Result	Reference
Toxicity to green algae, *Selenastrum capricomutum*, growth inhibition test	OECD201	72 hour $NOEC_{growth\ rate}$ = 30 mg/L 72 hour $LOEC_{growth\ rate}$ = 60 mg/L 72 hour $EC50_{growth\ rate}$ = 94 mg/L 72 hour $NOEC_{biomass}$ = 15 mg/L 72 hour $LOEC_{biomass}$ = 30 mg/L 72 hour $EC50_{biomass}$ = 46 mg/L	3
	OECD202		4

Acute toxicity to *Daphnia magna*		48 hour NOEC = 55 mg/L 48 Hour EC50 = 144 mg/L	
Acute toxicity to rainbow trout, *Oncohynchus mykiss*	OECD203	96 hour NOEC = 120 mg/L 96 hour EC50 > 120 mg/L	5

Predicted No Effect Concentration (PNEC)

Short-term test have been undertaken for species from three trophic levels, based on internationally accepted guidelines. The most sensitive species of these is the green alga, *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capriocornutum*), and the growth rate end point has been applied. Therefore, the PNEC is based on the growth rate results (EC50) from the toxicity to *P subcapitata* study, and an assessment factor of 1000 is applied in accordance with ECHA guidance (Ref 6).

PNEC = 94 000/1000 = 94 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.000050 µg/L /94 µg/L = $0.5*10^{-7}$
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 formoterol fumarate dihydrate has been considered to result in insignificant environmental risk”.

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

Environmental Fate Data

Study Type	Method	Result	Reference
Aerobic biodegradation	ISO 8727-1984E	20.5% biodegradation after 28 days. Not readily biodegradable	6

Physical Chemistry Data

Study Type	Method	Result	Reference
Octanol-water distribution coefficient	Shake flask	pH 5 $\log D_{OW}$ = 0.146 pH 7 $\log D_{OW}$ = 1.18 pH 9 $\log D_{OW}$ = 7.85	7
Dissociation Constant	Potentiometric titration	pKa = 7.9 (Phenol) pKa = 9.2 (Amine)	8

Biodegradation

Based on the data above and lack of further studies, the phrase “Formoterol fumarate dihydrate is potentially persistent” is chosen.

In Swedish: “Formoterol fumarat dihydrat är potentiellt persistent ” under the heading ”Nedbrytning”.

Bioaccumulation

Partition coefficient Octanol/Water
Log D = 1.18 at pH 7

Since Log D < 4 the phrase ‘Formoterol fumarate dihydrate has low potential for bioaccumulation’ is assigned.

In Swedish: ”Formoterol fumarat dihydrat har låg potential att bioackumuleras” under the heading ”Bioackumulering”.

References

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