FASS

Gardette forte

M

AstraZeneca

Inhalationspulver 320 mikrogram/9 mikrogram/inhalation
(Tillhandahålls ej)

Aktiva substanser (i bokstavsordning):

Budesonid
Formoterol

ATC-kod:

R03AK07

Läkemedel från AstraZeneca omfattas av Läkemedelsförsäkringen
.

Miljöpåverkan

Budesonid

Miljörisk: Risk för miljöpåverkan av budesonid kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.
Nedbrytning: Budesonid bryts ned i miljön.
Bioackumulering: Budesonid har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC/PNEC = 0.008µg/L /8.60µg/L = 0.00092

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 = $1.37* 10^{-6} *57.657 * (100-0)$ **= 0.008 µg/L**

A (Kg/year) = total sold amount API in Sweden year 2021, data from IQVIA/Lif.
= 57.657 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). As such, environmental exposure of budesonide resulting from patient use is expected to be negligible; however the PEC does not take into consideration metabolism and therefore provides a worst-case exposure senario.

PNEC (Predicted No Effect Concentration)

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
Toxicity to green algae, *Selenastrum capricornutum* growth inhibition test	OECD 201	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	4

Study Type	Method	Result	Reference
		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 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	5

Study Type	Method	Result	Reference
		72 hour EC50 (biomass) > 7.9 mg/L	
Daphnia magna reproduction test under semi-static conditions	OECD 211	21 day NOEC = 6.95mg/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, *Oncorhynchus mykiss*	OECD 203	96 hour LC50 (mortality) > 13 mg/L 96 hour NOEC (mortalitiy) = 13mg/L	8
Fish Life cycle test *Danio rerio*	Bespoke	F0 generation Early life stage: NOEC ≥ 3200 ng/L hatch, day 28 survival and length	9

Study Type	Method	Result	Reference
		Juvenile growth stage: NOEC = 1000 ng/L length at day 56 (mechanistically appropriate NOEC) NOEC ≥ 3200 ng/L survival Reproduction: NOEC ≥ 3200 ng/L based on time to spawning, total egg number, eggs/female and fertilization rate Test termination: NOEC ≥ 3200 ng/L for survival, length, weight, sex ratio, vitellogenin, 11-keto-testosterone F1 generation	

Study Type	Method	Result	Reference
		Early life stage: NOEC = 32 ng/L survival at day 28 (conservative NOEC) NOEC ≥ 3200 ng/L hatch, length and dry weight	
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 (sediment dry weight)	10

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

Environmental risk classification (PEC/PNEC ratio)

Data from both long and short-term ecotoxicology studies are available for Budesonide to derive a PNEC. As per ECHA guidelines (ref 11), the preferable method to derive the PNEC is to apply an assessment factor to the long-term data. In this case, long term data is available for three trophic levels (ref. 4, 5, 6 & 9) which includes a fish full life cycle study.

The fish full life cycle study with zebrafish was purchased from a third party as part of a post approval commitment for a Budesonide containing product. AstraZeneca maintains that the overall quality of the study is questionable and the results observed are uncertain and inconsistent.

In the reported fish life-cycle test no significant effects on reproduction were
observed in the F0-generation. There were also no observed effects on the two biomarkers, vitellogenin and 11-keto testosterone concentrations, in blood plasma. Histopathological evaluation of female fish gonads showed an increase of ovum debris and inflammation of ovary tissue, which was considered to have impacted on egg quality at 1000 ng/L and above. However, the biological relevance remains unclear since there was no significant impact on the apical reproduction endpoints; time to spawning, total egg production, eggs per female, fertilisation rate, or hatching.

There was no impact on male gonad morphology. There were no statistically significant effects on the F0 hatching success nor the early life-stage (day 28)

survival or length endpoints. A statistically significant effect for F0 length in the 3200 ng/L concentration was observed at day 56, however this was transient and no significant differences in length were observed at termination of the F0 generation. There were also no significant effects on survival or sex ratio at the termination of the F0 generation. However, when separated by sex, a statistically significant effect on weight was observed at 3200 ng/L in female fish, only.

In the F1-generation, there were no statistically significant effects on hatching success or early life-stage growth (day 28 weight and length). There was a reduction in F1 survival at a concentration of 100 ng/L Budesonide at day 28. Although this was statistically significant, the result is a net loss of one fish compared to control, there was no clear dose response at higher concentrations and the biological mechanism of action is unknown. Further, it appears that the control fish may have performed better than typical for that laboratory, leaving the reliability open to significant questions.

The lowest NOEC from this study, the day 28 survival NOEC of 32 ng/L, based on specific survival effects in the F1-generation fish has no known mode of action and is considered overly conservative. The growth effect (NOEC = 1000 ng/L), albeit limited to females and to the weight parameter only, is considered more mechanistically appropriate and is therefore proposed as a more relevant, yet still conservative endpoint.

In conclusion, there were no effects on reproduction endpoints considered to be related to administration of Budesonide in this study. Survival of the F1-generation was determined to be the most sensitive endpoint driving the overall study NOEC. Yet, it is

considered that the lack of dose response and potential effects of study design on the statistical outcome have impacted the ability to interpret the data. However, in line with the regulatory environmental risk assessment and to take a precautionary approach, the day 28 survival NOEC of 32 ng/L is taken as the overall NOEC for the study.

To calculate the $PNEC_{conservative}$ using the day 28 survival NOEC of 32ng/L (equivalent to 0.032µg/L) an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 11).

$PNEC_{conservative}$ = 0.032/10 = 0.0032 µg/L

For data comparison purposes, an additional, mechanistically appropriate PNEC is also derived from the fish study, using the NOEC for female weight (1000 ng/L), to better characterise the risk of Budesonide. To calculate the $PNEC_{mechanistic}$ using the mechanistically appropriate NOEC of 1000ng/L (equivalent to 1µg/L) an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 11).

$PNEC_{mechanistic}$ = 1/10 = 0.1 µg/L

Prior to the purchase of the fish life cycle study, only acute data was available for three trophic levels. For all three species, the EC50 values were greater than the highest test concentration and the limit of solubility of budesonide in the test medium. To further scrutinize the data collected, a PNEC value based on acute data is also considered, using the lowest limit of solubility of budesonide in the test media, reported for the algal study. The PNEC is based on

the lowest >EC50 value of 8.6mg/L (equivalent to 8600ug/L) and an assessment factor of 1000 is applied, in accordance with ECHA guidance (Ref. 11).

$PNEC_{acute}$ = 8600/1000 = 8.6 µg/L

Environmental risk classification (PEC/PNEC ratio)

As discussed, there are three proposed PNECs available to calculate the PEC/PNEC ratio, as shown in the table below.

	PNEC	PEC	PEC/PNEC ratio	Environmental Risk
$PNEC_{conservative}$	0.0032	0.008	2.5	moderate
$PNEC_{mechanistic}$	0.1		0.08	insignificant
$PNEC_{acute}$	8.6		0.0009	insignificant

It is acknowledged that the worst case data in the table above is generated from the $PNEC_{conservative}$, however due to the unreliability of the fish full life cycle study it is deemed inappropriate to define the environmental risk of Budesonide using this value. As the $PNEC_{mechanistic}$ is also generated from data collected in the same study, it is therefore not possible to justify the use of this value to assign the environmental risk statement.

Despite the unreliability of the data collected in the fish full life cycle study, the available data does point toward a chronic sensitivity to fish therefore it is also not appropriate to use the $PNEC_{acute}$ data to conclude the environmental risk.

Due to the questionable reliability of the fish full life cycle study, AstraZeneca outsourced a new study in 2020. Until this new data is available, it is concluded that there is insufficient data available to assess environmental impact of Budesonide at this time. Data is expected to be available from this study by Q3 2023, at which point a PNEC can be derived to assign an environmental risk statement.

This justifies the use of:
Risk of environmental impact of Budesonide cannot be excluded, since there is not sufficient ecotoxicity data available.
In Swedish: Risk för miljöpåverkan av Budesonide kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.

Environmental Fate Data

Environmental Fate Data for Budesonide

Study Type	Method	Result	Reference
Determination of ready biodegradability	OECD301F	Degradation after 28 days <2.2 % Not readily biodegradable	12
	OECD106		13

Study Type	Method	Result	Reference
Adsorption/desorption to sediments, soils and sludge		Mean ± SD Kd (ads) (5 soils) = 34.6 ± 16.6 Mean ± SD Koc (ads) (5 soils) = 1629 ± 1734	
Aerobic transformation in aquatic sediment systems	OECD308	HOM DT50 (water) = 6.9 days LOM DT50 (water) = 6.45 days HOM DT50 (total system) = 18.1 days* LOM DT50 (total system) = 12.5 days HOM 14CO2 (98 DAT) = 54.8% AR LOM 14CO2 (98 DAT) = 86.2% AR <15% of applied radioactivity remaining as parent compound (0%	14

Study Type	Method	Result	Reference
		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

Biotic 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 14CO2 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 DT50 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 carp *Cyprinus carpio*	OECD305	BCF_L at 3µg/L = 9 ± 3 Not bioaccumulative in fish	17

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 the BCF was reported <500 the phrase “Budesonide has low potential for bioaccumulation” is assigned.

In Swedish: Budesonid har låg potential att bioackumuleras.

References

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4. Budesonide: Toxicity to the green alga Selenastrum capricornutum. Bowles A.J. Brixham Environmental Laboratory Report BL8078/B. May 2005.
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7. Budesonide: Acute toxicity to Daphnia magna. Bowles A.J. Brixham Environmental Laboratory Report BL8079/B. May 2005.
8. Budesonide: Acute toxicity to rainbow trout (Oncorhynchus mykiss). Bowles A.J. Brixham Environmental Laboratory Report BL8080/B. May 2005.
9. Budesonide: A Life cycle test with the Zebrafish (Danio rerio) under flow through conditions. Dipl. Ing. Matthias Teigeler. Fraunhofer Institute for Molecular Biology and Applied Ecology IME. June 2014
10. Sediment-water chironomid toxicity test using sediment spiked with Budesonide. M.J.E. Desmares-Koopmans, Bachelor, ERT. Charles River Laboratories Den Bosch B.V. Project 509587. July 2016.

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14. [4-^{14}C]Budesonide – Degradation in Two Different Aquatic Systems under Aerobic and Anaerobic Conditions. Dr. Rafal Piskorski. Innovative Environmental Services (IES) Ltd. May 2016.
15. Budesonid - preformuleringsrapport. Report no. 83 – 014. Draco, Lund, Sweden. 1 February 1983.
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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Formoterol

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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