

Budfor

AstraZeneca

Inhalationspulver 80 mikrogram/4,5 mikrogram/inhalation

Avregistreringsdatum: 2013-11-30 (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

Budesonid

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

$$\text{PEC/PNEC} = 0.00904 \mu\text{g/L} / 0.09 \mu\text{g/L} = 0.1004$$

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):

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

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

$$\text{PEC} = 1.37 \cdot 10^{-6} \cdot 65.9603 \cdot (100 - 0)$$

$$= \mathbf{0.00904 \mu\text{g/L}}$$

A (Kg/year) = total sold amount API in Sweden year 2023, data from IQVIA/Lif.

$$= 65.9603 \text{ kg/year}$$

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

P = number of inhabitants in Sweden = $10 \cdot 10^6$ (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 |
| Toxicity to green algae, <i>Selenastrum capricornutum</i> 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 (b iomass) = 5.6 mg/L 72 hour LOEC (bi omass) = 8.6 mg/L 72 hour EC50 (bi omass) > 8.6 mg/L | |
| Growth inhibition study <i>Pseudokirchneriella subcapitata</i> (previously <i>Selenastrum capricornutum</i>) | OECD 201 | 72 hour NOEC (g rowth rate) = 7.9 mg/L 72 hour LOEC (g rowth rate) > 7.9 mg/L 72 hour EC50 (gr owth rate) > 7.9 mg/L 72 hour NOEC (b iomass) = 7.9 mg/L 72 hour LOEC (bi omass) > 7.9 mg/L | 5 |

| Study Type | Method | Result | Reference |
|---------------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------|-----------|
| | | 72 hour EC50 (biomass) > 7.9 mg/L | |
| <i>Daphnia magna</i> 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, <i>Daphnia magna</i> | OECD 202 | 48 hour EC50 (immobility) >14 mg/L 48 hour NOEC (immobility) = 3.8mg/L | 7 |
| Acute toxicity to Rainbow Trout, <i>Oncorhynchus mykiss</i> | OECD 203 | 96 hour LC50 (mortality) > 13 mg/L 96 hour NOEC (mortality) = 13mg/L | 8 |
| Life-cycle toxicity test with the Zebrafish, <i>Danio rerio</i> | 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 | 9 |

| Study Type | Method | Result | Reference |
|-----------------------------------------------------------------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| | | 180/181 day LOEC _(Male wet weight and length; F0 larval survival) = 2.8µg/L | |
| Toxicity to sediment dwelling midge, <i>Chironomus riparius</i> | 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

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).

$$\text{PNEC} = 0.9 \mu\text{g/L} / 10 = 0.09 \mu\text{g/L}$$

Environmental risk classification (PEC/PNEC ratio)

$$\text{PEC/PNEC} = 0.00904 \mu\text{g/L} / 0.09 \mu\text{g/L} = 0.1004$$

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 \pm SD Kd (ads) (5 soils) = 34.6 \pm 16.6 Mean \pm SD Koc (ads) (5 soils) = 1629 \pm 1734 | 13 |
| | OECD308 | | 14 |

| Study Type | Method | Result | Reference |
|----------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Aerobic transformation in aquatic sediment systems | | <p>HOM DT₅₀ (water) = 6.9 days</p> <p>LOM DT₅₀ (water) = 6.45 days</p> <p>HOM DT₅₀ (total system) = 18.1 days*</p> <p>LOM DT₅₀ (total system) = 12.5 days</p> <p>HOM ¹⁴C₂ (98 DAT) = 54.8% AR</p> <p>LOM ¹⁴C₂ (98 DAT) = 86.2% AR</p> <p><15% of applied radioactivity remaining as parent compound (0% in water + 3.8%* in sediment) at the end of the study</p> | |

* 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 K_d values ranged from 20 to 66 L/kg, with a derived mean of 34.6 L/kg. The corresponding K_{oc} 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 $^{14}\text{CO}_2$ 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 $\text{DT}_{50} \leq 32d$ 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°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, <i>Cyprinus carpio</i> | 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 (BCF_{ss}) 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

1. Fass.se (2012). Environmental classification of pharmaceuticals at www.fass.se: Guidance for pharmaceutical companies
https://www.fass.se/pdf/Environmental_classification_of_pharmace
2. Investigator's Brochure. Drug Substance Budesonide/formoterol. Project Code D589000000. Edition Number 9. Date 31 May 2016.
3. Budesonide: Activated sludge respiration inhibition test. R Harrigan & P Curtis-Jackson. Brixham Environmental Laboratory Report No BR0451/B. May 2011
4. Budesonide: Toxicity to the green alga *Selenastrum capricornutum*. Bowles A.J. Brixham Environmental Laboratory Report BL8078/B. May 2005.
5. Budesonide: Toxicity to green algae *Pseudokirchneriella subcapitata* determined in a growth inhibition study. Erica Tediosi, Desirée Garagna. ChemService S.r.l. Controlli e Ricerche Report 165/2013. July 2013.
6. Budesonide: *Daphnia magna* reproduction test under semi-static conditions. Erica Tediosi. ChemService S.r.l. Controlli e Ricerche Report 164/2013. September 2013.
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 flow-through life-cycle toxicity test with the zebrafish (*Danio rerio*). Easton study number 123A-139. Eurofins EAG Agrosience, LLC. Maryland, USA. May 2023.
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.
11. ECHA (European Chemicals Agency) 2008. Guidance on information requirements and chemical safety assessment. Chapter R.10: Characterisation of dose [concentration]-response for environment http://guidance.echa.europa.eu/docs/guidance_document/informa
12. Budesonide: Ready biodegradability in a manometric respirometry test. Erica Tediosi ChemService S.r.l. Controlli e Ricerche Report CH-166/2013. July 2013
13. Budesonide: Determination of the adsorption / desorption coefficient Koc. Stefano Paronuzzi Ticco. ChemService S.r.l. Controlli e Ricerche Report 190/2013. September 2013.
14. [4-¹⁴C]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.

17. Bioaccumulation in fish with Budesonide (flow-through, aqueous exposure). L.M. Bouwman, MSc. Charles River Den Bosch B.V. Project 509585. August 2016

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

$$\text{PEC/PNEC} = 0.000050 \mu\text{g/L} / 94 \mu\text{g/L} = 0.5 \cdot 10^{-7}$$

$$\text{PEC/PNEC} \leq 0.1$$

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

The PEC is based on the following calculation:

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

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

$$\text{PEC} = 1.37 \cdot 10^{-6} \cdot 0.34 \cdot (100 - 0)$$

$$= \underline{0.000050 \mu\text{g/L}}$$

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

= $10 \cdot 10^6$

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, <i>Selenastrum capricornutum</i> , growth inhibition test | OECD201 | 72 hour NOEC_{gr} growth rate = 30 mg/L 72 hour LOEC_{gro} growth rate = 60 mg/L | 3 |

| | | | |
|------------------------------------------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| | | 72 hour EC50 _{gro} with rate = 94 mg/L 72 hour NOEC _{bio} mass = 15 mg/L 72 hour LOEC _{bio} mass = 30 mg/L 72 hour EC50 _{bio} mass = 46 mg/L | |
| Acute toxicity to <i>Daphnia magna</i> | OECD202 | 48 hour NOEC = 4 55 mg/L 48 Hour EC50 = 144 mg/L | |
| Acute toxicity to rainbow trout, <i>O</i> <i>ncohynchus</i> <i>mykiss</i> | OECD203 | 96 hour NOEC = 5 120 mg/L 96 hour EC50 > 120 mg/L | |

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).

$$\text{PNEC} = 94\,000/1000 = 94 \mu\text{g/L}$$

Environmental risk classification (PEC/PNEC ratio)

$$\text{PEC/PNEC} = 0.000050 \mu\text{g/L} / 94 \mu\text{g/L} = 0.5 \cdot 10^{-7}$$

$$\text{PEC/PNEC} \leq 0.1$$

The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase, and the risk phrase for $\text{PEC/PNEC} \leq 0.1$ 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 | $\text{pH } 5 \log D_{\text{OW}} = 0.146$ | 7 |

| | | | |
|-----------------------|--------------------------|--------------------------------------------------------------|----------|
| | | pH 7 $\log D_{OW} =$ 1.18 pH 9 $\log D_{OW} =$ 7.85 | |
| 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

1. [ECHA] European Chemicals Agency. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.16: Environmental exposure assessment (version 3.0). February 2016.
2. Determination of absolute pulmonary bioavailability of formoterol when given via Turbuhaler® to healthy volunteers. Report No. 37-CR-3004. January 1995.
3. Formoterol Fumarate Dihydrate: Toxicity to the green alga *Selenastrum capricornutum*. Brixham Environmental Laboratory, AstraZeneca, UK. Report BL8081 (2005).
4. Formoterol Fumarate Dihydrate: Acute toxicity to *Daphnia magna*. Brixham Environmental Laboratory, AstraZeneca, UK Report BL8082 (2005).
5. Formoterol Fumarate Dihydrate: Acute toxicity to Rainbow Trout (*Oncorhynchus mykiss*). Brixham Environmental Laboratory, AstraZeneca, UK. Report BL8083 (2005).
6. A026: Biodegradability. Report no: 59/93, Toxicon, Landskrona, Sweden. 10 January 1994
7. Determination of the n-octanol/Water Partition Coefficient of Formoterol Fumarate by the Shake Flask Method, 123K-104, EAG, Inc., Easton, Maryland 2017
8. Marketing, S1-03 general Properties, Formoterol Fumarate Dihydrate. AstraZeneca report BD4179 (2009).