

## **Bofunir**

### **Sandoz AS**

Inhalationspulver, avdelad dos 320 mikrogram/9  
mikrogram/inhalation

Avregistreringsdatum: 2023-06-15 (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 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

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

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

### 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

$$= 0.34 \text{ kg}$$

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  $\mu\text{g}$ .

## 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 $\text{NOEC}_{\text{gr}}$ growth rate = 30 mg/L 72 hour $\text{LOEC}_{\text{gro}}$ growth rate = 60 mg/L 72 hour $\text{EC50}_{\text{gro}}$ growth rate = 94 mg/L	3

		72 hour NOEC <sub>bio</sub> mass = 15 mg/L 72 hour LOEC <sub>bio</sub> mass = 30 mg/L 72 hour EC50 <sub>bio</sub> 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>Oncorhynchus 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)

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

PEC/PNEC  $\leq$  0.1

The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase, and the risk phrase for 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	<b>6</b>

### 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 $\log D_{OW} = 7.85$	<b>7</b>

Dissociation Constant	Potentiometric titration	pKa = 7.9 (Phenol) pKa = 9.2 (Amine)	<b>8</b>
-----------------------	--------------------------	-----------------------------------------------	----------

## 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).