

## Tecfidera

MR<sub>x</sub>F<sub>f</sub>

### Biogen Sweden

Enterokapsel, hård 120 mg

(Oval kapsel, grön och vit, märkt "BG-12 120 mg" 7,0 x 21,0mm)

Övriga medel med verkan på nervsystemet

### Aktiv substans:

Dimetylfumarat

### ATC-kod:

L04AX07

Läkemedel från Biogen Sweden omfattas av Läkemedelsförsäkringen.

Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

## Miljöpåverkan

### Dimetylfumarat

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

Nedbrytning: Dimetylfumarat bryts ned i miljön.

Bioackumulering: Dimetylfumarat har låg potential att bioackumuleras.

### Detaljerad miljöinformation

### Detailed background information

### Environmental Risk Classification

### Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

$$PEC (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100) = 1.5 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

$$PEC = 0.029 \mu\text{g/L}$$

Where:

A = 194.8145 kg (total sold amount API in Sweden year 2015, data from IMS Health).

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation). This is considered a conservative value.

P = number of inhabitants in Sweden =  $9 \cdot 10^6$

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

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

## Predicted No Effect Concentration (PNEC)

### Ecotoxicological studies

*Algae (Pseudokirchneriella subcapitata)* (OECD 201) (Ref. 2):

EC50 72h (growth rate) > 1 800 µg/mL

NOEC (growth rate) = 37 µg/mL

*Crustacean (Daphnia magna)*:

Chronic toxicity (OECD 211) (Ref. 3)

NOEC 21 days (reproduction) = 55.9 µg/mL

*Fish (Pimephales promelas)*:

Chronic toxicity (OECD 210) (Ref. 4)

NOEC 28 days (survival) = 45.7 µg/mL

*Other ecotoxicity data:*

Calculation of PNEC is obtained by applying assessment factors (AF) to long-term ecotoxicity data (Ref 1):

Lowest NOEC/AF

$PNEC = 3.7 \mu\text{g/L}$

Where:

Lowest NOEC = 37 µg/mL (*Pseudokirchneriella subcapitata*, growth inhibition test)

AF = 10 based on the availability of chronic toxicity studies for three trophic levels

### Environmental risk classification (PEC/PNEC ratio)

$PEC/PNEC = 0.029/3.7 = 0.0078$ , i.e.  $PEC/PNEC \leq 0.1$  which justifies the phrase "Use of dimethyl fumarate has been considered to result in insignificant environmental risk."

## Degradation

### Biotic degradation

*Ready degradability:*

*Test results showed* > 60% degradation within five days (OECD 301) (Ref 5).

*Justification of chosen degradation phrase:*

Dimethyl fumarate passes the ready degradability test, hence the degradation phrase should be: "*Dimethyl fumarate is degraded in the environment.*"

### Bioaccumulation

*Partitioning coefficient:* Log Pow = 0.74 at neutral pH (experimentally determined with unknown method) (Ref 6).

Since log Pow < 4 at pH 7, dimethyl fumarate is considered to have "low potential for bioaccumulation".

### Excretion (metabolism)

In humans, dimethyl fumarate is extensively metabolised with less than 0.1% of the dose excreted as unchanged dimethyl fumarate in urine. Exhalation of CO<sub>2</sub> is the primary route of dimethyl fumarate elimination accounting for 60% of the dose. Renal and faecal elimination are secondary routes of

elimination, accounting for 15.5% and 0.9% of the dose respectively. Primary active metabolite is monomethyl fumarate (Ref 7.).

## References

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[http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
2. Internal document: Smithers Viscient Study No. 3200151. Anderson M. Inhibition of growth to the alga *Pseudokirchneriella subcapitata*. Report issued April 2013. Smithers Viscient (ESG) Ltd., Harrogate, North Yorkshire, United Kingdom.
3. Internal document: Covance Study No. 8253806. Last G. Dimethyl fumarate: Chronic effects to *Daphnia magna*. Report issued January 2012. Covance Laboratories, Harrogate, North Yorkshire, United Kingdom.
4. Internal document: Covance Study No. 8253807. Last G. Dimethyl fumarate: Fish early life stage test (*Pimephales promelas*). Report issued January 2012. Covance Laboratories, Harrogate, North Yorkshire, United Kingdom.
5. Environmental risk assessment, CTD module 1.6 of "Tecfidera"
6. Hansch C., et al. 1995, Chem ID+, US National Library of Medicine, National Institute of Health, <http://chem.sis.nlm.nih.gov> <https://chem.nlm.nih.gov/chemidplus/name/dimethyl%20fumarate>
7. Tecfidera SmPC 2016-11-17, <http://www.ema.europa.eu>