Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Zanamivir	**Relenza**

Executive Summary

GSK is committed to ensuring that our compounds do not adversely affect the environment. We carry out state-of-the-art environmental testing on all our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to the environment. The results of these assessments suggest that no adverse environmental impact is likely to result from post-patient release of GSK pharmaceuticals into the environment.

This Environmental Risk Assessment (ERA) has been conducted for zanamivir and a risk to the environment has not been excluded due to insufficient ecotoxicity data. Therefore, the Predicted Environmental Concentration (PEC) to Predicted No Effects Concentration (PNEC) ratio has not been calculated.

*GlaxoSmithKline's public position statement on pharmaceuticals in the environment may be accessed via this link - **GlaxoSmithKline's Position: Pharmaceuticals in the Environment**.*

The following pages contain the technical background information.

Technical Background Information

Environmental Fate

This substance is water soluble and is not likely to partition to air from water very readily. Zanamivir is not lipophilic and therefore has low potential to bioconcentrate in exposed aquatic organisms. Zanamivir is not readily nor inherently biodegradable and is expected to be persistent. Based on water solubility and a low adsorption coefficient this substance is unlikely to adsorb to sludge or biomass and is not expected to reach the terrestrial compartment to a significant extent. The fraction of zanamivir which reaches the terrestrial environment will be subject to moderate degradation.

PEC/PNEC Risk Quotient Calculation

European Union

The PEC/PNEC risk quotient calculation is the standard quantitative method of risk assessment and is approved by major national and international regulatory agencies [2, 3, 4].

Predicted Environmental Concentration

The PEC has been calculated based on the following data:

$$\text{PEC } (\mu g/L) = \frac{A \times 1E+09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of zanamivir active based on sales in the European Union in 2012 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For zanamivir it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the European Union (EU 27) = 502.48 x 10^6 (IMS Data).

V (L/day) = volume of wastewater per capita and day = 200, EMA default [2].

D = factor for dilution of waste water by surface water flow = 10, EMA default [2].

NB: PEC, conservatively, is based on no metabolism and no removal of drug substance to sludge solids. It is assumed that 100% of drug substance enters the aquatic environment.

PEC = 0.0000027 µg/L

Predicted No Effects Concentration (PNEC)

A PNEC may not be calculated because ecotoxicity data from all three trophic levels of aquatic organisms is not available.

PNEC = Not applicable

PEC/PNEC Risk Characterisation

PEC/PNEC $_{\text{(European Union)}}$ = Not determined

PEC/PNEC Risk Quotient Calculation

United States of America

The PEC/PNEC risk quotient calculation is the standard quantitative method of risk assessment and is approved by major national and international regulatory agencies [2, 3, 4].

Predicted Environmental Concentration

The PEC has been calculated based on the following data:

$$\text{PEC } (\mu g/L) = \frac{A \times 1E+09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of zanamivir active based on sales in the United States in 2012 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For zanamivir it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the United States of America = 311.591 x 10^6 (IMS Data).

V (L/day) = volume of wastewater per capita and day = 370, USGS.

D = factor for dilution of waste water by surface water flow = 10, FDA default [5].

NB: PEC, conservatively, is based on no metabolism and no removal of drug substance to sludge solids. It is assumed that 100% of drug substance enters the aquatic environment.

PEC = 0.00017 µg/L

Predicted No Effects Concentration (PNEC)

A PNEC may not be calculated because ecotoxicity data from all three trophic levels of aquatic organisms is not available.

PNEC = Not applicable

PEC/PNEC Risk Characterisation

PEC/PNEC (United States of America) = Not determined

All relevant environmental fate and ecotoxicity data are published in Section 12 of the Material Safety Data Sheet (MSDS) for the medical product. The MSDS is publicly available at http://www.msds-gsk.com/ExtMSDSlist.asp.

Metabolism and Excretion

Zanamivir has been shown to be renally excreted as unchanged drug, and does not undergo metabolism. In vitro studies demonstrated that zanamivir did not affect the activity of a range of probe substrates for cytochrome P450 isoenzymes (CYP1A/2, A6, 2C9, 2C18, 2D6, 2E1, 3A4) in human hepatic microsomes, nor did it induce cytochrome P450 expression in rats, suggesting that metabolic interactions between zanamivir and other drugs are unlikely in vivo. The serum half-life of zanamivir following administration by oral inhalation ranges from 2.6 to 5.05 hours. It is entirely excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 L/h as approximated by urinary clearance. Renal elimination is completed within 24 hours [1].

References

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