Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Lamivudine	Epivir
	Epzicom
	Trizivir
	Combivir

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 lamivudine and demonstrates that the use of this drug substance is considered to result in insignificant environmental risk. This evaluation is based on the Predicted Environmental Concentration (PEC) to Predicted No Effects Concentration (PNEC) ratio of less than 0.1. Lamivudine is an active ingredient in GSK pharmaceutical products and pharmaceutical products sold by other companies. This assessment takes account of the total quantity of active ingredient marketed by GSK and all other companies.**

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 has solubility in water and is not likely to partition to air from water very readily. Lamivudine is not readily nor inherently biodegradable and is expected to persist in the environment. Lamivudine is not lipophilic and has a low potential to bioconcentrate in exposed aquatic organisms. Significant removal from the aquatic environment by sorption to sludge solids in wastewater treatment plants and surface water sediments is not expected.

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 lamivudine active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 93% of this market in 2013.

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

P = number of inhabitants in the European Union (EU 27) = 500.151 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 = 0.037 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (μg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for algae (= 96,900 μg/L) has been used for this calculation since it is the most sensitive of the tested species.

PNEC = 96,900/50 = 1,938 μg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.037/1,938

PEC/PNEC (European Union) = 0.000019

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:

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

where:

A (kg/year) = total use of lamivudine active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 86% of this market in 2013.

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

P = number of inhabitants in the United States of America = 321.489×10^6 (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 = 0.024 μg/L

Predicted No Effects Concentration (PNEC)

PNEC (μg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for algae (= 96,900 μg/L) has been used for this calculation since it is the most sensitive of the tested species.

PNEC = 96,900/50 = 1,938 μg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.024/1,938

PEC/PNEC (United States of America) = 0.000012

The PEC/PNEC is ≤ 0.1 which means the use of lamivudine in the United States of America is considered to result in insignificant environmental risk, in accordance with the fass environmental classification scheme [4].

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

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding [1].

References

1. Summary of Product Characteristics Epivir (lamivudine) 300mg tablets. GlaxoSmithKline, May 2014. http://www.medicines.org.uk/EMC/

2. Committee for Medicinal Products for Human Use (CHMP); Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 1 June 2006, Ref EMEA/CPMP/SWP/4447/00. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf

3. European Chemicals Agency (ECHA). 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

4. Fass Environmental Classification of Pharmaceuticals. 2012 Guidance for Pharmaceutical Companies. www.fass.se

5. Food and Drug Administration (FDA). 1998 Guidance for Industry on Environmental Assessment of Human Drug and Biologics Applications. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf