Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Aciclovir	**Zovirax**
Valaciclovir	**Valtrex**

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 aciclovir 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. Aciclovir 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

ERA Note

Valaciclovir is the prodrug of aciclovir and is rapidly and almost completely converted in man to aciclovir. As a result this ERA takes account quantity of active aciclovir derived from all products containing valaciclovir as this is the active ingredient which predominantly enters the environment. Accordingly, this ERA takes account of total aciclovir volumes from all products containing aciclovir and valaciclovir as active ingredients.

Environmental Fate

Aciclovir is not readily biodegradable and is not susceptible to hydrolysis and is therefore expected to persist in the environment. However, this substance is inherently biodegradable. Significant removal of aciclovir is expected to occur in wastewater treatment plants due to biodegradation. This substance has limited water solubility and a low partition coefficient suggests it is unlikely to bioconcentrate in exposed aquatic organisms.

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 [3, 4, 5].

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 aciclovir active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 9.52% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For aciclovir it has been assumed that R = 0% as a worst case scenario [4].

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 [3].

D = factor for dilution of waste water by surface water flow = 10, EMA default [3].

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 = 0.47 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 water flea (= 10,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 10000/50 = 200 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.47/200

PEC/PNEC (European Union) = 0.0024

The PEC/PNEC is ≤ 0.1 which means the use of aciclovir in the European Union is considered to result in insignificant environmental risk, in accordance with the fass environmental classification scheme [5].

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 [3, 4, 5].

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 aciclovir active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 1.13% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For aciclovir it has been assumed that R = 0% as a worst case scenario [4].

P = number of inhabitants in the United States of America = 321.489 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 [6].

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 = 0.74 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 water flea (= 10,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 10000/50 = 200 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.74/200

PEC/PNEC (United States of America) = 0.0037

The PEC/PNEC is ≤ 0.1 which means the use of aciclovir in the United States of America is considered to result in insignificant environmental risk, in accordance with the fass environmental classification scheme [5].

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

In adults the terminal plasma half-life of aciclovir after administrations of intravenous aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration contributes to the renal elimination of the drug. 9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for approximately 10 - 15% of the administered dose recovered from the urine [1].

After oral administration, valaciclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9(carboxymethoxy)methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolized by cytochrome P450 enzymes. Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the aciclovir metabolite CMMG (about 14% of the recovered dose). The metabolite 8-OH-ACV is detected only in small amounts in urine (< 2% of the recovered dose). Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug [2].

References

1. Summary of Product Characteristics Zovirax (acyclovir) Tablets. GlaxoSmithKline, December 2013. http://www.medicines.org.uk/EMC/
2. Summary of Product Characteristics Valtrex (valaciclovir hydrochloride) Tablets. GlaxoSmithKline,April 2014. http://www.medicines.org.uk/EMC/

3. 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
4. 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
5. Fass Environmental Classification of Pharmaceuticals. 2012 Guidance for Pharmaceutical Companies. www.fass.se
6. 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