Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Nelarabine	**Arranon** **Atriance**

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 nelarabine 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.

*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. Nelarabine is not readily nor inherently biodegradable and is expected to persist in the environment. This material slowly undergoes biodegradation in soil. Nelarabine 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 nelarabine 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 nelarabine 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 = 0.000011 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest EC50/1000, where 1000 is the assessment factor applied for three acute EC50s. EC50 for alga and fish (=100,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 100,000/1,000 = 100 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.000011/100

PEC/PNEC (European Union) = 0.00000011

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 nelarabine active based on sales in the United States of America in 2012 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For nelarabine 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 = 0.000095 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest EC50/1000, where 1000 is the assessment factor applied for three acute EC50s. EC50 for alga and fish (= 100 mg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 100,000/1,000 = 100 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.000095/100

PEC/PNEC (United States of America) = 0.0000095

The PEC/PNEC is ≤ 0.1 which means the use of nelarabine 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

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G. Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate metabolite. The monophosphate metabolite is subsequently converted to the active 5'-triphosphate from, ara-GTP. The principal route of metabolism for nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolysed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Nelarabine and ara-G are partially eliminated by the kidneys. In 28 adult patients, 24 hours after nelarabine infusion on day 1, mean urinary excretion of nelarabine and ara-G was 5.3 % and 23.2 % of the administered dose, respectively. Renal clearance averaged 9.0 l/h/m2 (151 %) for nelarabine and 2.6 l/h/m2 (83%) for ara-G in 21 adult patients [1].

References

1. Summary of Product Characteristics Atriance (nelarabine) solution for infusion. GlaxoSmithKline, April 2013. 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