Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Sodium stibogluconate	**Pentostam**

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 sodium stibogluconate 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. Sodium stibogluconate is not lipophilic and therefore has low potential to bioconcentrate in exposed aquatic organisms. The potential for persistence of Sodium stibogluconate cannot be excluded due to lack of degradation data. Based on water solubility and a low partition coefficient this substance is unlikely to adsorb to sludge or biomass and is not expected to reach the terrestrial compartment to a significant extent.

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 sodium stibogluconate 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 sodium stibogluconate 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 = 0.0000055 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 (Not applicable)

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 sodium stibogluconate 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 sodium stibogluconate 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 = 0.0 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

Following intravenous or intramuscular administration of sodium stibogluconate, antimony is excreted rapidly via the kidneys, the majority of the dose being detected in the first 12-hour urine collection. This rapid excretion is reflected by a marked fall in serum or whole blood antimony levels to approximately 1 to 4% of the peak level by 8 hours after an intravenous dose. During daily administration, there is a slow accumulation of sodium stibogluconate into the central compartment so that tissue concentrations reach a theoretical maximum level after at least 7 days [1].

References

1. Summary of Product Characteristics Pentostam (Sodium stibogluconate) Injection. GlaxoSmithKline, August 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