Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Rosiglitazone	**Avandia** **Avandamet** **Avandaryl**

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 rosiglitazone 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

Rosiglitazone is not readily biodegradable but is inherently biodegradable and has been shown to be chemically unstable in water. It is expected not to persist in the environment. This substance is water soluble and a low partition coefficient suggests it is unlikely to bioconcentrate in exposed aquatic organisms. Significant removal from the aquatic environment by biodegradation in wastewater treatment plants is expected. It is not likely 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 (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 rosiglitazone 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 rosiglitazone 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 = 0.00 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for water flea (= 100 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 100/10 = 10 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = Not applicable

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 rosiglitazone 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 rosiglitazone 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 = 0.0000071 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for water flea (= 100 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 100/10 = 10 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0000071/10

PEC/PNEC (United States of America) = 0.00000071

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

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or intravenous administration of [14C] rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [14C] related material ranged from 103 to 158 hours [1].

References

1. Human Prescription Drug Label Avandia (Rosiglitazone maleate) tablets. GlaxoSmithKline, April 2012. http://dailymed.nlm.nih.gov/dailymed
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