Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Carvedilol	**Coreg**
	Coreg CR

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 carvedilol 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. Carvedilol 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 limited water solubility and is not likely to partition to air from water very readily. It is not lipophilic and does not have a high potential for bioconcentration in exposed aquatic organisms. Carvedilol is not readily biodegradable but is inherently biodegradable. Significant removal from the aquatic environment by biodegradation in wastewater treatment plants is expected. It is likely to adsorb to sludge or biomass and is expected to reach the terrestrial compartment to a significant extent where it is predicted to sorb extensively and irreversibly to soil matrices.

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:

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

where:

A (kg/year) = total use of carvedilol active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 0% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For carvedilol 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 = 0.0 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 (= 250 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 250/50 = 5 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0/5

PEC/PNEC (European Union) = 0.00

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 carvedilol active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 7% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For carvedilol 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 = 0.060 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 (= 250 μg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 250/50 = 5 μg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.06/5

PEC/PNEC (United States of America) = 0.012

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

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade. Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent [1].

References

1. Human Prescription Drug Label Coreg (Carvedilol) tablets. GlaxoSmithKline, July 2011. 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