Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Clobetasol propionate	**Dermovate**

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 clobetasol propionate 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. Clobetasol propionate 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

Clobetasol propionate is not readily biodegradable nor inherently biodegradable and has limited solubility in water. It is expected to persist in the environment. A moderate partition coefficient suggests that clobetasol has a low potential to bioconcentrate in exposed aquatic organisms. Moderate removal from the aquatic environment by sorption to sludge solids in wastewater treatment plants and surface water sediments is 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 clobetasol propionate active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 51% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For clobetasol propionate 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 = 0.00073 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 fish (= 750 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 750/1000 = 0.75 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00073/0.75

PEC/PNEC (European Union) = 0.00098

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 clobetasol propionate active based on total sales (GSK + all other companies) in the United States of America 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 clobetasol propionate 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 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 = 0.00 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 fish (= 750 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 750/1000 = 0.75 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0/0.75

PEC/PNEC (United States of America) = 0.0

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 percutaneous absorption of clobetasol propionate, the drug probably follows the metabolic pathway of systemically administered corticosteroids, i.e. metabolised primarily by the liver and then excreted by the kidneys. However, systemic metabolism of clobetasol has never been fully characterised or quantified [1].

References

1. Summary of Product Characteristics Dermovate cream (Clobetasol propionate). GlaxoSmithKline, December 2007. 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
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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