Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Fluticasone propionate	**Cutinate** **Flixonase** **Flixotide** **Flonase** **Flovent**

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 fluticasone propionate and a risk to the environment has not been excluded based on limited ecotoxicity data. However, this substance has the potential to affect non-standard environmental endpoints through its specific mechanism of action. GSK is presently conducting a tailored risk assessment strategy that will address the specific mechanism of action (potential endocrine disruptor) associated with this pharmaceutical. This ERA will be updated when relevant data become available.

*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. Fluticasone propionate is not lipophilic and does not have the potential for bioconcentration in exposed aquatic organisms. Fluticasone propionate is not readily biodegradable or inherently biodegradable and therefore the fraction of this substance which partitions to the aquatic environment will persist. However, this substance likely to adsorb to sludge or biomass and is expected to reach the terrestrial compartment to a significant extent where it will be subject to slow biodegradation.

Fluticasone propionate is a glucocorticoid and as such has the potential for endocrine disruption in exposed organisms. This substance therefore has the potential to affect non-standard developmental and reproductive endpoints in environmental species. GSK is presently conducting a tailored risk assessment strategy that will address the specific mechanism of action (potential endocrine disruptor) associated with this pharmaceutical. This ERA will be updated when relevant data become available.

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 fluticasone propionate active based on sales in the European Union in 2013 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For fluticasone propionate it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the European Union (EU 27) = 500.151×10^6 (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 = 0.00352 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

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 fluticasone propionate active based on sales in the United States of America in 2013 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For fluticasone 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 = 0.00147 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

Fluticasone propionate does not persist in any tissue, and does not bind to melanin. The major route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group, to yield a carboxylic acid (GR36264), which has very weak glucocorticoid or anti-inflammatory activity. In all test animal species, the route of excretion of radioactivity is independent of the route of administration of radiolabelled fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours. In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus drug entering the systemic circulation via the skin, will be rapidly inactivated. Oral bioavailability approaches zero, due to poor absorption and extensive first-pass metabolism. Therefore systemic exposure to any ingestion of the topical formulation will be low [1].

References

1. Summary of Product Characteristics Cutivate(Fluticasone propionate) Cream 0.05%. GlaxoSmithKline, 27 February 2014. http://www.medicines.org.uk/EMC/
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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