Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Fluticasone furoate	**Avamys** **Veramyst**

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 furoate 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 furoate is not lipophilic and does not have the potential for bioconcentration in exposed aquatic organisms. Fluticasone furoate 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.

Fluticasone furoate 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 furoate 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 furoate 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 = 0.000090 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 furoate 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 furoate 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 = 0.0000069 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 furoate is rapidly cleared (total plasma clearance of 58.7 l/h) from systemic circulation principally by hepatic metabolism to an inactive 17β-carboxylic metabolite (GW694301X), by the cytochrome P450 enzyme CYP3A4. The principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate function to form the 17β-carboxylic acid metabolite. In vivo studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone. Elimination was primarily via the faecal route following oral and intravenous administration indicative of excretion of fluticasone furoate and its metabolites via the bile. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Urinary excretion accounted for approximately 1 % and 2 % of the orally and intravenously administered dose, respectively faeces [1].

References

1. Summary of Product Characteristics Avamys (Fluticasone furoate). GlaxoSmithKline, June 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