15 December 2022

Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Fluticasone furoate	**Avamys** **Relvar Ellipta** **Trelegy Ellipta**

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 our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to the environment. We post summaries of our Environmental Risk Assessments on the GSK website as part of our commitment to data transparency.

This Environmental Risk Assessment (ERA) has been conducted for Fluticasone furoate 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. Ranitidine 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.

The following pages contain the technical background information.

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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 is 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 has conducted a tailored risk assessment that has addressed the specific mechanism of action (potential endocrine active substance) associated with this pharmaceutical.

PEC/PNEC Risk Quotient Calculation

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 (GSK + all other companies) in the European Union in 2021 (IQVIA 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 = Population of European Union + UK. Per capita use of drug substance A/P = 2.57E-07 kg/inhabitant (IQVIA Data).

V (L/day) = volume of wastewater per capita and day = 200, EMA default [2].

D = factor for dilution of wastewater 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 = 0.00035 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for one long-term NOEC but where there is a high degree of confidence that the dataset includes the most sensitive species (fish). On this basis the NOEC for fish (0.58 µg/L) has been used in the calculation.

PNEC = 0.58/10 = 0.058 µg/L

PNEC Justification

Fluticasone furoate is a glucocorticoid and, as such, is considered as a potential endocrine active substance. Therefore, the potential endocrine activity of this compound was investigated in an appropriate chronic vertebrate test system with relevant end points. Accordingly, GSK has conducted a fish early life-stage test, as per OECD 210, as a range-finder to set concentrations for an extended early life-stage test, exposing newly fertilised embryos until they reached sexual maturity (OECD 234). This study concluded that no statistically significant effects were observed between the controls and any of the test concentrations in terms of hatching success, post-hatch survival, growth, spawning ability or secondary sexual characteristics. Due to the mode of action of fluticasone furoate and its potential to act as an endocrine active substance there is a high degree of confidence that fish is the most sensitive species and, on that basis, there is a strong justification for applying an AF of 10 [3].

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00035/0.058

PEC/PNEC = 0.006

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

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 2021. 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. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.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 v3.0 Guidance for Pharmaceutical Companies. www.fass.se