29 April 2022

Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Vilanterol trifenatate	**Anoro Ellipta** **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 Vilanterol 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. Vilanterol 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.

29 April 2022

Technical Background Information

Environmental Fate

Vilanterol is practically insoluble in water and is not likely to partition to air from water very readily. It is not readily nor inherently biodegradable and is not expected to be extensively mineralized (converted to CO2). This substance has a low partition coefficient which suggests it is unlikely to bioconcentrate in exposed aquatic organisms.

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 (PEC)

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 Vilanterol based on patient consumption in the European Union and UK in 2020 (IQVIA Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For Vilanterol 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 = 2.93E-08 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 = 0.00004 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fish (= 370 ug/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 370/10 = 37 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00004/37

PEC/PNEC = 0.0000011

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

Vilanterol is In vitro studies showed that vilanterol is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic routes for vilanterol are O-dealkylation to a range of metabolites with significantly reduced beta1- and beta2-adrenergic agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low. Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral administration of radiolabelled vilanterol, mass balance showed 70% of the radiolabel in urine and 30% in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces. Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours [1].

References

1. Summary of Product Characteristics Anoro Ellipta (55ug/22ug umeclidinium bromide/ vilanterol trifenatate) inhalation powder. GlaxoSmithKline, April 2021. http://www.medicines.org.uk/EMC/
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   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