

Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Umeclidinium bromide	Anoro Ellipta Incruse 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 Umeclidinium bromide 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. Umeclidinium bromide 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.

Technical Background Information

Environmental Fate

Umeclidinium bromide is slightly water soluble 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:

$$\text{PEC } (\mu\text{g/L}) = \frac{A \times 1\text{E} + 09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of Umeclidinium bromide based on patient consumption in the European Union and UK in 2021 (IQVIA Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For Umeclidinium bromide 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 = 2.73E-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 = 0.000037 µg/L

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fish (= 125 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

$$\text{PNEC} = 125/10 = 12.50 \mu\text{g/L}$$

PEC/PNEC Risk Characterisation

$$\text{PEC/PNEC} = 0.000037/12.50$$

$$\text{PEC/PNEC} = 0.0000030$$

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

In vitro studies showed that umeclidinium bromide is principally metabolised by cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium bromide are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium bromide plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% active substance excreted unchanged in urine at steady-state [1].

References

1. Summary of Product Characteristics Anoro Ellipta (55ug/22ug umeclidinium bromide/Vilanterol trifenate) inhalation powder. GlaxoSmithKline, April 2021.
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http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
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