15 December 2022

# Environmental Risk Assessment Data Summary

| *Active Pharmaceutical Ingredient* | *Medical Product* |
|---|---|
| **Dutasteride** | **Avodart**<br>**Combodart** |

## 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 Dutasteride 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. Dutasteride 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

Dutasteride is not readily biodegradable nor inherently biodegradable and has limited solubility in water. It is expected to persist in the environment. A moderate partition coefficient suggests that dutasteride has a moderate potential to bioconcentrate in exposed aquatic organisms. Significant removal from the aquatic environment by sorption to sludge solids in wastewater treatment plants and surface water sediments is expected.

## 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 Dutasteride 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 Dutasteride 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 = 8.47E-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 = 0.0012 µg/L**

## Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor applied for one long-term NOECs 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 (21 µg/L) has been used in the calculation.

**PNEC = 21/50 = 0.42 µg/L**

## PNEC Justification

An extended Fish ELS study was conducted to investigate the potential of dutasteride, as a 5 alpha reductase inhibitor, to indirectly act as an endocrine disruptor. This modified fish early life stage toxicity test (OECD 210) examined the dose-effect relationship between aquatic dutasteride concentration and the development of secondary sexual characteristics and effects on gonad development in fish. Appropriate LOEC and NOEC values have been generated. Due to the mode of action of dutasteride and the potential receptor-mediated effects there is a high degree of confidence that fish is the most sensitive species from the species base set and on that basis there is a strong justification for applying an AF of 50 [3].

## PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0012/0.42

**PEC/PNEC = 0.0029**

The PEC/PNEC is ≤ 0.1 which means the use of dutasteride in the European Union 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

Dutasteride is extensively metabolized in vivo. In vitro, dutasteride is metabolized by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite. Following oral dosing of dutasteride 0.5 mg/day to steady state,

1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each). Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine [1].

## References


1. Summary of Product Characteristics Avodart capsules (Dutasteride). GlaxoSmithKline, April 2020. 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