Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Dutasteride	**Avodart** **Combodart** **Duodart**

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 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.

*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

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

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 dutasteride active based on sales in the European Union in 2012 (IMS 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 = number of inhabitants in the European Union (EU 27) = 502.48 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 = 0.00058 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 = 0.00058/0.42

PEC/PNEC $_{\text{(European Union)}}$ = 0.0014

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].

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 dutasteride active based on sales in the United States of America in 2012 (IMS 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 = number of inhabitants in the United States of America = 311.591 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 = 0.00021 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

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00021/0.42

PEC/PNEC (United States of America) = 0.0005

The PEC/PNEC is ≤ 0.1 which means the use of dutasteride in the United States of America 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

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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