Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Ropinirole	**Requip** **Adartrel**

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 ropinirole 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. Ropinirole 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.

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

Ropinirole is not readily nor inherently biodegradable and is not susceptible to hydrolysis. It is expected to persist in the environment. This substance is water soluble and a low partition coefficient suggests it is unlikely to bioconcentrate in exposed aquatic organisms. Removal from the aquatic environment by sorption to sludge solids in wastewater treatment plants and surface water sediments is not expected to be significant.

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 ropinirole active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 55% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For ropinirole it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the European Union (EU 27) = 500.151 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 = 0.0017 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for water flea (= 3,200 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 3,200/50 = 64 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0017/64

PEC/PNEC (European Union) = 0.000027

The PEC/PNEC is ≤ 0.1 which means the use of ropinirole 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 ropinirole active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 2% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For ropinirole it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the United States of America = 321.489 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 = 0.0011 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/50, where 50 is the assessment factor applied for two long-term NOECs. NOEC for water flea (= 3,200 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 3,200/50 = 64 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0011/64

PEC/PNEC (United States of America) = 0.000017

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

Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. The increase in systemic exposure (Cmax and AUC) to ropinirole is approximately proportional over the therapeutic dose range. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed [1].

References

1. Summary of Product Characteristics Requip (ropinirole hydrochloride) Tablets. GlaxoSmithKline, February 2014. 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. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.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 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