Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Argatroban	**Argatroban Injection**

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 argatroban 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. Argatroban 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

Argatroban is not readily biodegradable or inherently biodegradable. 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. It is not likely to adsorb to sludge or biomass and is not expected to reach the terrestrial compartment to a significant extent.

PEC/PNEC Risk Quotient Calculation

European Union (Not applicable)

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 argatroban active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 0% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For argatroban 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 = 0.0 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest EC50/1000, where 1000 is the assessment factor applied for three short-term EC50s. EC50 for water flea (= 52,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 52,000/1000 = 52 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = Not Applicable

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 argatroban active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 49% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For argatroban 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 = 0.000051 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest EC50/1000, where 1000 is the assessment factor applied for three short-term EC50s. EC50 for water flea (= 52,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 52,000/1000 = 52 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.000051/52

PEC/PNEC (United States of America) = 0.00000098

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

The main route of Argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the 4 known metabolites is catalyzed in vitro by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than Argatroban. Unchanged Argatroban is the major component in plasma. The plasma concentrations of M1 range between 0% and 20% of that of the parent drug. The other metabolites (M2 to M4) are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on Argatroban pharmacokinetics, suggest that CYP3A4/5-mediated metabolism is not an important elimination pathway in vivo.

Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which 14C-Argatroban (5 mcg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces [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