Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Sumatriptan	**Treximet** **Imigran** **Imitex**

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 sumatriptan 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. Sumatriptan 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

This substance has limited solubility in water and is not likely to partition to air from water very readily. Sumatriptan is not readily nor inherently biodegradable and is not susceptible to hydrolysis. It is expected to persist in the environment. However, significant removal of sumatriptan is expected to occur in wastewater treatment plants via primary biodegradation. This substance has a low partition coefficient which suggests it is unlikely to bioconcentrate in exposed aquatic organisms. It is likely to adsorb to sludge or biomass and is expected to reach the terrestrial compartment to a moderate extent. This material slowly undergoes biodegradation in soil.

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 sumatriptan active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 24% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For sumatriptan 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 = 0.001 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/50, where 1000 is the assessment factor applied for three short-term NOECs. NOEC for green algae (= 26,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 26,000/50 = 520 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.001/520

PEC/PNEC $_{\text{(European Union)}}$ = 0.0000019

The PEC/PNEC is ≤ 0.1 which means the use of sumatriptan 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 sumatriptan active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 5% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For sumatriptan 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 = 0.017 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/50, where 1000 is the assessment factor applied for three short-term NOECs. NOEC for green algae (= 26,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 26,000/50 = 520 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.017/520

PEC/PNEC (European Union) = 0.000033

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

Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT1 or 5-HT2 activity. Minor metabolites have not been identified [1].

References

1. Summary of Product Characteristics Imigran (sumatriptan succinate) Injection. GlaxoSmithKline, August 2013. http://www.medicines.org.uk/EMC/
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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