# Environmental Risk Assessment Data Summary

| *Active Pharmaceutical Ingredient* | *Medical Product* |
|---|---|
| **Naratriptan** | **Naramig** |

## 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 naratriptan 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. Naratriptan 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 solubility in water and is not likely to partition to air from water very readily. Naratriptan is not readily nor inherently biodegradable and is expected to persist in the environment. Naratriptan is not lipophilic and has a low potential to bioconcentrate in exposed aquatic organisms. Moderate removal from the aquatic environment by sorption to sludge solids in wastewater treatment plants and surface water sediments is expected. It is likely to adsorb to sludge or biomass and is expected to reach the terrestrial compartment to a moderate extent.

## 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 naratriptan active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 48% of this market in 2013.

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For naratriptan 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 = 0.000077 µg/L**

## Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/1000, where 1000 is the assessment factor applied for three short-term NOECs. NOEC for fish (= 100,000 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

**PNEC = 100,000/1,000 = 100 µg/L**

## PEC/PNEC Risk Characterisation

PEC/PNEC = 0.000077/100

**PEC/PNEC (European Union) = 0.00000077**

# PEC/PNEC Risk Quotient Calculation

## *United States of America (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

GSK does not market naratriptan in the United States. Therefore, the PEC has not been calculated:

$$\text{PEC } (\mu g/L) = \frac{A \times 1E+09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of naratriptan active based on total sales (GSK + all other companies) in the United States of America 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 naratriptan 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 = 0.0 µg/L**

### Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/1000, where 1000 is the assessment factor applied for three short-term NOECs. NOEC for water flea (= 100 mg/L) has been used for this calculation since it is the most sensitive of the three tested species.

**PNEC = 100,000/1,000 = 100 µg/L**

## PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0/100

**PEC/PNEC (United States of America) = 0.00**

**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

Naratriptan is predominantly excreted in the urine with 50% of the dose recovered as unchanged naratriptan and 30% recovered as inactive metabolites [1].

## References

1. Summary of Product Characteristics Naramig (naratriptan hydrochloride) tablets. GlaxoSmithKline, July 2013. 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