Environmental Risk Assessment Data Summary

Active Pharmaceutical Ingredient	*Medical Product*
Retigabine	**Trobalt**

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 retigabine 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

Retigabine is not readily nor inherently biodegradable and is not susceptible to hydrolysis. It is expected to persist in the environment. However, significant removal of retigabine is expected to occur in wastewater treatment plants via primary biodegradation and sorption to sludge solids. This substance has limited solubility in water and a low partition coefficient suggests it is unlikely to bioconcentrate in exposed aquatic organisms.

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 retigabine 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 retigabine it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the European Union (EU 27) = 502.48×10^6 (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 = 0.0015 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fathead minnow (= 32 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 32/10 = 3.20 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.108/6.20

PEC/PNEC $_{\text{(European Union)}}$ = 0.00047

The PEC/PNEC is ≤ 0.1 which means the use of retigabine 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 retigabine 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 retigabine 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 = 0.00034 µg/L

Predicted No Effects Concentration (PNEC)

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fathead minnow (= 32 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 32/10 = 3.20 µg/L

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00034/3.20

PEC/PNEC (United States of America) = 0.00011

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

Retigabine is extensively metabolised in humans. A substantial fraction of the retigabine dose is converted to inactive N-glucuronides. Retigabine is also metabolised to an N-acetyl metabolite (NAMR) that is also subsequently glucuronidated. NAMR has antiepileptic activity, but is less potent than retigabine in animal seizure models. There is no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes. Therefore co-administration with inhibitors or inducers of cytochrome P450 enzymes is unlikely to affect the pharmacokinetics of retigabine or NAMR.

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (36%). Only 14% of retigabine is excreted in the faeces [1].

References

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4. Fass Environmental Classification of Pharmaceuticals. 2012 Guidance for Pharmaceutical Companies. www.fass.se
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