

Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Dolutegravir sodium	Dovato Juluca Tivicay Triumeq

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 our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to the environment. We post summaries of our Environmental Risk Assessments on the GSK website as part of our commitment to data transparency.

This Environmental Risk Assessment (ERA) has been conducted for Dolutegravir 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.

The following pages contain the technical background information.

Technical Background Information

Environmental Fate

Dolutegravir is slightly water soluble and is not likely to partition to air from water very readily. It is not readily nor inherently biodegradable and is not expected to be extensively mineralized (converted to CO₂). However, moderate removal of the parent by primary degradation is expected at the STP. While this substance is not lipophilic at neutral pH, a relatively high water/sludge distribution coefficient (K_{oc}) suggests it will significantly partition to the terrestrial environment. Although this substance is considered to be persistent it is expected to be relatively immobile in the aquatic and terrestrial environment.

PEC/PNEC Risk Quotient Calculation

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 (PEC)

The PEC has been calculated based on the following data:

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

where:

A (kg/year) = total use of Dolutegravir active based on sales in the European Union in 2021 (IQVIA Data).

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

P = Population of European Union + UK. Per capita use of drug substance A/P = 8.53E-06 kg/inhabitant (IQVIA Data).

V (L/day) = volume of wastewater per capita and day = 200, EMA default [2].

D = factor for dilution of wastewater 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 = 0.012 µg/L

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for green alga (= 95.40 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

$$\text{PNEC} = 95.40/10 = 9.54 \mu\text{g/L}$$

PEC/PNEC Risk Characterisation

$$\text{PEC/PNEC} = 0.012/9.54$$

$$\text{PEC/PNEC} = 0.0012$$

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

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low ($< 1\%$ of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose). Dolutegravir has a terminal half-life of ~ 14 hours. The apparent oral clearance (CL/F) is approximately 1L/hr in HIV-infected patients based on a population pharmacokinetic analysis [1].

References

1. Summary of Product Characteristics Tivicay (dolutegravir) 10mg tablets. GlaxoSmithKline, October 2021. <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.
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.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 v3.0 Guidance for Pharmaceutical Companies. www.fass.se