Environmental Risk Assessment Data
Esomeprazole and Omeprazole

The data below refer both to esomeprazole and omperazole, as esomeprazole is the *S*-enantiomer of the racemate omeprazole. Only short term acute toxicity data are available for omeprazole, however the more scientifically robust long-term data set for esomeprazole provides a Predicted No Effect Concentration (PNEC) which is an order of magnitude lower. Therefore, the PNEC derived for esomeprazole is also applied to omeprazole and the predicted environmental concentration (PEC) is calculated from the total sales of both omeprazole and esomeprazole (and their respective salt forms).

Esomeprazole and omeprazole are proton pump inhibitors (PPIs) for the treatment of acid-related diseases.

Esomeprazole is an active pharmaceutical ingredient used in Nexium and Vimovo. Omeprazole is an active pharmaceutical ingredient used in Gastroloc, Mopral, Omepral and Prilosec.

After administration, esomeprazole and omeprazole are almost completely metabolised, with <1% found in urine as the parent compound. Approximately 80% of the metabolites are excreted by urine and approximately 20% via faeces. The two main excreted human metabolites are both excreted via urine, and are considerably less pharmacologically active than the parent compounds.

Based on the physical-chemical and fate properties, esomeprazole and omeprazole are not predicted to be readily biodegraded during wastewater treatment. However, esomeprazole is rapidly degraded in aquatic sediment systems, which suggests that both compounds will be degraded in the aquatic environment. In addition, neither esomeprazole nor omeprazole are predicted to bioaccumulate in aquatic organisms.

The PEC / PNEC ratio for esomeprazole is 0.013, which means use of both esomeprazole and omeprazole is predicted to present an insignificant risk to the environment.

Predicted Environmental Concentration (PEC) of Esomeprazole and Omeprazole (combined)
The PEC is based on the following data:

$PEC\ (\mu g/L) = (A*10^9*(100-R))/(365*P*V*D*100)$

A (kg/year) = total patient consumption of esomeprazole and omeprazole (active moieties) in the European country with the highest per capita use in 2016 (Source: IMS Health[1])
R (%) = % removal during wastewater (sewage) treatment (due to loss by adsorption to sludge particles, by volatilisation, hydrolysis or biodegradation). It is assumed that R = 0 as a worst case.
P = number of inhabitants in the country with the highest per capita use (Source: EuroStat[2]).
$A/P = 9.3 \times 10^{-4}$ kg/inhabitant
V (L/day) = volume of wastewater per capita and day = 200 (European Medicines Agency (EMA) default value, Ref. 1)
D = factor for dilution of waste water by surface water flow = 10 (Ref 1)
(Note: The factor 10^9 in the equation above converts the quantity used from kg to µg)

PEC = 1.3 µg/L

[1] IMS Health, MIDAS International Data for 2016, available for 22 European markets
[2] The number of persons having their usual residence in a country on 1 January 2016. Available from http://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables Accessed: 20/4/17

Predicted No Effect Concentration (PNEC) Esomeprazole and Omeprazole
Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the lowest NOEC value 1 mg/L (equivalent to 1,000 µg/L) which was reported for *Pimephales promelas* and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 2). For the purpose of this risk assessment it is assumed that the same PNEC applies to omeprazole.

PNEC = 1,000 µg/L /10 = 100 µg/L

PEC/PNEC Esomeprazole and Omeprazole (combined)
PEC = 1.3 µg/L
PNEC = 100 µg/L

PEC/PNEC = 0.013

The PEC/PNEC ratio of 0.013 corresponds to the phrase 'Use of the substance has been considered to result in low environmental risk' in the www.fass.se scheme (Ref 3).

Environmental Fate Summary
Esomeprazole (and omeprazole) is almost completely metabolised after administration. In the aquatic environment, both esomeprazole and omeprazole are likely to be rapidly degraded. Neither compound is readily biodegradable. That the substances will partition into, and degrade rapidly within, aquatic sediments. Based on the octanol-water partition coefficient it is unlikely that the compounds will bioaccumulate in aquatic organisms.

Aquatic Toxicity Data for Esomeprazole

Study Type	Method	Result	Ref
Activated sludge, respiration inhibition test	OECD209	3 h EC50 >100 mg/L 3 h NOEC = 100 mg/L	4
Toxicity to green algae, *Selenastrum capricornutum*, growth inhibition test	OECD201	72 h $NOEC_{growth\ rate}$ = 8.4 mg/L 72 h $LOEC_{growth\ rate}$ = 19 mg/L 72 h $EC50_{growth\ rate}$ = 85 mg/L 72 h $NOEC_{biomass}$ = 3.9 mg/L 72 h $LOEC_{biomass}$ = 8.4 mg/L 72 h $EC50_{biomass}$ = 19 mg/L	5
Fish early-life stage toxicity with fathead minnow, *Pimephales promelas*	OECD210	32 d NOEC = 1.0 mg/L 32 d LOEC = 3.2 mg/L based on hatch, survival, length and weight	6
Chronic toxicity to *Daphnia magna*	OECD211	21 d NOEC = 10 mg/L 21 d LOEC > 10 mg/L based on reproduction and length	7
Long-term toxicity to *Chironomus riparius*	OECD218	28 d NOEC = 400 mg/kg 28 d LOEC = 1000 mg/kg dry sediment, based on emergence, development rate and sex ratio	8

EC50 the concentration of the test substance that results in a 50% effect
NOEC no observed effect concentration
LOEC lowest observed effect concentration

Environmental Fate Data for Esomeprazole

Study Type	Method	Result	Ref
Aerobic biodegradation	OECD301C	<0.6% after 28 days. Not readily biodegradable	9
Adsorption/desorption to sludge	OPPTS guideline 835.1110	Kd(ads) = 48 Kd(des) was calculated as 242 (however data was variable)	10
Aerobic transformation in aquatic sediment systems	OECD308	High organic matter test system DT50 = 2.2 d in water, 3.1 d total system Low organic matter test system DT50 = 3 d in water, 6.3 d total system After 100 days of incubation, less than 1 % of parent material remained in the aqueous phase and less than 5 % remained in the extractable sediments of both test systems. At day 100 no single transformation product was present at >10% of the applied radioactivity.	11

Physical Chemistry Data for Esomeprazole

Study Type	Method	Result	Ref
Octanol-water distribution coefficient	OECD117, HPLC	pH 5 = 1.65 pH 7 = 1.58 pH 9 = 1.53	12
Water solubility	-	300 mg/L (esomeprazole) at pH 7	-
Hydrolysis	-	Half-life at 25°C = 20 h, pH 6.8 Half-life at 37°C = 10 h, pH 6.8	13

Aquatic Toxicity Data for Omeprazole

Study Type	Method	Result	Ref
Activated sludge, respiration inhibition test	OECD209	3 h EC50 >100 mg/L 3 h NOEC = 100 mg/L	17
Toxicity to green algae, *Selenastrum capricornutum*, growth inhibition test	OECD201	72 h $NOEC_{growth\ rate}$ = 1.8 mg/L 72 h $EC50_{growth\ rate}$ > 76 mg/L 72 h $NOEC_{biomass}$ <1.8 mg/L 72 h $EC50_{biomass}$ = 30 mg/L	14
Acute toxicity to *Daphnia magna*	OECD202	48 h EC50 > 100 mg/L based on immobility	15
Acute toxicity to zebra fish, *Danio rerio*	OECD203	96 hour LC50 = 42 mg/L (mortality)	16

EC50 the concentration of the test substance that results in a 50% effect
LC50 the concentration of the test substance that results in a 50% mortality
NOEC no observed effect concentration

Environmental Fate Data for Omeprazole

Study Type	Method	Result	Ref
Aerobic biodegradation	OECD301C	<0% degradation after 28 days. Not readily biodegradable	17

Physical Chemistry Data for Omeprazole

Study Type	Method	Result	Ref
Octanol-water distribution coefficient	Unknown	Log D (experimental) = 2.24	18
Water solubility		130 mg/L	
Dissociation Constant		$pKa_{(1)}$ = 4 (Pyridinium ion) $pKa_{(2)}$ = 8.8 (Benzimidazole ion)	

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