Boehringer Ingelheim

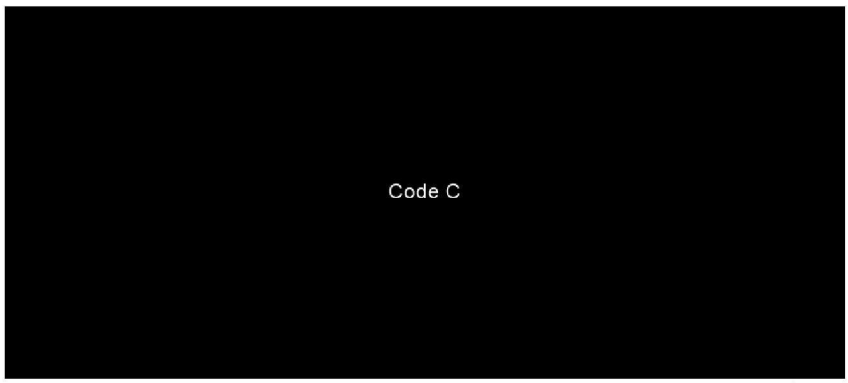
Environmental Risk Assessment (ERA)

Substance: Tiotropium bromide **Title: Environmental Risk Assessment of Spiriva® Respimat® 2.5 microgram, inhalation solution**	**Document Number** **ra00803460** **18 April 2016** **Page 1 of 5**

AUTHENTICATION

I, the undersigned, hereby declare that this statement was prepared under my supervision.

Reporting:



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1. INTRODUCTION

This Type II variation is for the extension of the indication to include treatment of asthma in paediatric patients. According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00, June 2006) the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use.

2. STATEMENT ON THE ENVIRONMENTAL RISK ASSESSMENT

Tiotropium bromide is an anticholinergic agent administered by inhalation for the maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD) and asthma.

Spiriva® Respimat® 2.5 microgram, inhalation solution is approved in all 30 EU/EA countries with the following indications:

COPD
"Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD)".

Asthma
Spiriva Respimat is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting β_2 agonists and who experienced one or more severe exacerbations in the previous year.

This Type II variation for Spiriva® Respimat® 2.5 microgram, inhalation solution refers to the following asthma indication:

Spiriva Respimat is indicated as add-on maintenance bronchodilator treatment in patients aged 1 year and older with asthma who remain symptomatic on treatments that include an inhaled corticosteroid.

The daily dosage of Spiriva® Respimat® 2.5 microgram, solution for inhalation in both indications (COPD and asthma) and all age groups, is 5 µg tiotropium, given as 2 puffs of 2.5 µg per day.

Phase I calculation of the Predicted Environmental Concentration (PEC)

Since the maximum daily dosage of tiotropium is only 5 µg (= 0.005 mg), the Predicted Environmental Concentration (PEC) is calculated, to demonstrate that the potential environmental increase in the use of the substance is expected to be negligible.

The $PEC_{surface\ water}$ for Spiriva® Respimat® 2.5 microgram, solution for inhalation in Phase I is calculated using the default value for the market penetration (0.01).

$$\mathbf{PEC_{surface\ water}} = \frac{Dose(ai) \cdot Fpen}{Wastwater \cdot Dilution}$$

•	$PEC_{surface\ water}$	: *Predicted local surface water concentration*	[mg L^{-1}]
•	Dose (ai) = 0.005	: *Maximum daily dose of active ingredient consumed per inhabitant*	[mg d^{-1} inh^{-1}]
•	Wastewater = 200	: *Amount of wastewater per inhabitant per day (default)*	[L inh^{-1} d^{-1}]
•	Dilution = 10	: *Dilution factor (default)*	[-]
•	Fpen = 0.01	: *Fraction of the overall market penetration. The applicant may use the default value of 0.01 or refine the Fpen by providing reasonably justified market penetration data.*	[-]

The calculation of the $PEC_{surface\ water}$ results in $2 \cdot 10^{-11}$ µg/L.

As the $PEC_{surfacewater}$ value is clearly below 0.01 µg/L, calculated using the default value for the market penetration, even a Phase II environmental effect analysis is not required according to the above cited EMEA guideline.

Screening for persistence, bioaccumulation and toxicity (PBT assessment)

With reference to the OSPAR Convention, substances with an octanol/ water partition coefficient > 4.5 should be screened, in a step-wise procedure, for persistence, bioaccumulation and toxicity.

The experimentally determined octanol/ water partition coefficient for tiotropium bromide is -2.28 at pH 7.4 [1]. Since these values are clearly below the threshold of 4.5, an assessment of the potential of persistence, bioaccumulation and toxicity according to the OSPAR convention is not required.

Additional remark: The product does not contain genetically modified organisms (GMO). Thus, an ERA addressing GMO-specific risks is not applicable.

3. REFERENCES

[1] Physico-Chemical Characteristics of the Drug Substance Tiotropium Bromide Monohydrate in Solution (U00-1492)

4. APPENDIX

4.1 INFORMATION ON THE EXPERT

First Name and Surname:

Date of Birth:

Place of Birth:

Nationality:

Education:

Code C

Present Position: