

# **REGISTRATION REPORT**

## **Part B**

### **Section 10**

#### **Assessment of the relevance of metabolites in groundwater**

Detailed summary of the risk assessment

Product name(s): **INTUITY PLUS**  
(Mandestrobin 40 SC)

Chemical active substance:

Mandestrobin, 400 g/L

Central Zone

Zonal Rapporteur Member State: Poland

### **CORE ASSESSMENT**

(authorization)

Applicant: XXXX

Submission date: February 2024

Evaluation date: January 2025

Finalisation date: August 2025

## Version history

When	What
February 2024	Article 33 submission – Initial Applicant’s version
May 2024	- Update of the cover page with the product trade name ‘Intuity Plus’. Mandestrobin 40 SC is the internal unique name. The internal name Mandestrobin 40 SC is the one used across the dRR content.
January 2025	zRMS-PL evaluation
August 2025	Version revised to take into account cMSs’s comments

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## 10 Relevance of metabolites in groundwater

### 10.1 General information

The metabolites 5-COOH-S-2200 and 2-COOH-S-2200 are predicted to occur in groundwater at concentrations above 0.1 µg/L (see Part B section 8.8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.11 is therefore required. This has also been undertaken in previous Product assessments (AGES, 2016)

General information on the metabolites is provided in **Błąd! Nie można odnaleźć źródła odwołania..** The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter Chapter 8.8 - Predicted Environmental Concentrations in groundwater (PEC<sub>gw</sub>) of the dRR Part B, Section 8 (Environmental fate and behaviour).

#### Review Comments:

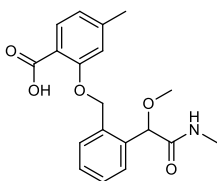
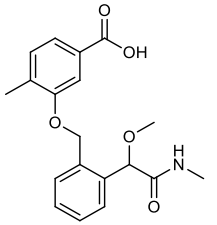
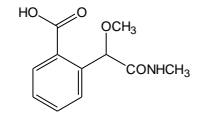
The trigger value of 0.1 µg/L was exceeded for metabolites of mandestrobin (please refer to Section B8). The relevant max PEC<sub>gw</sub> values are presented in Table 10.1-1.

The submitted data are accepted.

The mandestrobin metabolites 5-COOH-S-2200 and 2-COOH-S-2200 are considered non-relevant from the toxicological point of view based on the criteria identified in guidance document on the assessment of groundwater metabolites SANCO/221/2000 –rev.11.

The predicted maximum PEC<sub>gw</sub> for DX-CA-S-2200 are below 0.1 µg/L. Therefore a relevance assessment according to SANCO/221/2000 is not required.

**Table 10.1-1: General information on the metabolite(s)**

Active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Mandestrobin S-2200	2-COOH-S-2200		Max PEC <sub>gw</sub>	0.328 µg/L
			Based on:	Winter Oilseed Rape, soil with pH <sub>CaCl2</sub> ≥ 7.2 (Hamburg Scenario)
	5-COOH-S-2200		Max PEC <sub>gw</sub>	0.138 µg/L
			Based on:	Winter Oilseed Rape, soil with pH <sub>CaCl2</sub> ≥ 7.2 (Hamburg Scenario)
	DX-CA-S-2200		Max PEC <sub>gw</sub>	< 0.1 µg/L
		DX-CA-S-2200	Based on:	when considering application every other year (in scenarios relevant to the central zone)

## 10.2 Relevance assessment of 2-COOH-S-2200

The relevance of the groundwater metabolite 2-COOH-S-2200 has already been assessed and the assessment agreed at EU level (see EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015), and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the  $PEC_{gw}$  calculated for the GAP and groundwater scenarios considered in this dRR ). 2-COOH-S-2200 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11. A summary of the relevance assessment is given in **Błąd! Nie można odnaleźć źródła odwołania.** and the corresponding studies are listed in the corresponding sections.

**Table 10.2-1: Summary of the relevance assessment for 2-COOH-S-2200**

		Assessment step	Result of assessment		
		STEP 1	Metabolite of no concern?	no	
Quantification of groundwater contamination	STEP 2		Max PEC <sub>gw</sub>	0.328 µg/l Winter Oilseed Rape, soil with pH <sub>CaCl2</sub> ≥ 7.2	
			Based on	Hamburg Scenario	
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	no	Passes Stages 1-3 EFSA Journal 2015;13(5): 4100 and final addendum to the DAR, March 2015
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic based on Ames test (negative), <i>In vitro</i> chromosomal aberration test (negative, positive without S9 at cytotoxic levels), <i>in vitro</i> mammalian gene mutation assay (negative) and <i>in vivo</i> micronucleus assay (negative)	
		Stage 3	Toxic properties of metabolite;		
			Classification of parent	not classified as acutely or chronically toxic; not classified as reprotoxic; not classified as carcinogen	
			Classification of metabolite	not classified as acutely or chronically toxic; not classified as reprotoxic; not classified as carcinogen	
		Consumer health risk assessment	STEP 4		
STEP 5				Not required	

### 10.2.1 STEP 1: Exclusion of degradation products of no concern

2-COOH-S-2200 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

## 10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC<sub>gw</sub> calculations after leaching from soil for 2-COOH-S-2200 were performed (see Part B, Section 8, chapter 8.8). Maximum concentration is listed in **Błąd! Nie można odnaleźć źródła odwołania..** Details are given in Part B, Section 8, chapter 8.8.

## 10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

2-COOH-S-2200 has already been determined to be non-relevant at Step 3 (EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015).

## 10.2.4 STEP 4: Exposure assessment – threshold of concern approach

The PEC<sub>gw</sub> for 2-COOH-S-2200 was < 0.75 µg/L. There is no consumer exposure via other routes. 2-COOH-S-2200 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11.

## 10.2.5 STEP 5: Refined risk assessment

All PEC<sub>gw</sub> values are <0.75 µg/l.

## 10.3 Relevance assessment of 5-COOH-S-2200

The relevance of the groundwater metabolite 5-COOH-S-2200 has already been assessed and the assessment agreed at EU level (see EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015), and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PEC<sub>gw</sub> calculated for the GAP and groundwater scenarios considered in this dRR ). 5-COOH-S-2200 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11. A summary of the relevance assessment is given in **Błąd! Nie można odnaleźć źródła odwołania.** and the corresponding studies are listed in the corresponding sections.

**Table 10.3-1: Summary of the relevance assessment for 5-COOH-S-2200**

	Assessment step		Result of assessment		
	STEP 1		Metabolite of no concern?	No	
Quantification of groundwater contamination	STEP 2		Max PEC <sub>gw</sub>	0.138 µg/L Winter Oilseed Rape, soil with pH <sub>CaCl2</sub> ≥ 7.2	
			Based on	Hamburg Scenario	
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	no	

		Stage 2	Genotoxic properties of metabolite	Non-genotoxic based on Ames test (negative), <i>In vitro</i> chromosomal aberration test (negative) and in vitro mammalian gene mutation assay (negative)	Passes Stages 1-3 EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015
		Stage 3	Toxic properties of metabolite;		
			Classification of parent	not classified as acutely or chronically toxic; not classified as reprotoxic; not classified as carcinogen	
			Classification of metabolite	Acute toxicity: 300<oral LD <sub>50</sub> <2000 mg/kg bw; classified as Acute Tox. 4 not classified as acutely or chronically toxic; not classified as reprotoxic; not classified as carcinogen	
Consumer health risk assessment	STEP 4	Estimated consumer exposure via drinking water and other sources; threshold of concern approach		Acceptable (all scenarios < 0.75 µg/L)	
	STEP 5			Not required	

### 10.3.1 STEP 1: Exclusion of degradation products of no concern

5-COOH-S-2200 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

### 10.3.2 STEP 2: Quantification of potential groundwater contamination

PEC<sub>gw</sub> calculations after leaching from soil for 5-COOH-S-2200 were performed (see Part B, Section 8, chapter 8.8). Maximum concentration is listed in **Błąd! Nie można odnaleźć źródła odwołania..** Details are given in Part B, Section 8, chapter 8.8.

### 10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

5-COOH-S-2200 has already been determined to be non-relevant at Step 3 (EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015).

cMS's – DE comment provided during the commenting period:  
the metabolite meets the criteria for classification as acutely toxic, category 4 according to CLP Reg. No 1272/2008. Although this does not directly lead to the relevance of the metabolite.

Furthermore, as no acute oral toxicity was observed for the active substance up to 2000 mg/kg bw, it appears that the metabolite has a different toxicological profile and potentially higher toxicity compared to the parent substance, which should trigger further toxicological considerations. In this context Sanco/221/2000 – rev.11 states that “*However, independent of the classification of the parent active substance, if there is reason to expect that a certain degradation product may have toxicological hazards of concern, a targeted testing may be necessary.*”

In the acute oral toxicity study with 5-COOH-S-2200 effects were observed in the lung:

*“Retention of foamy fluid in the trachea was observed in 2 animals in the 2000 mg/kg bw group during the gross pathological examination. “Uncollapse” and pallor in all lobes of the lung were observed in one animal in the 300 mg/kg bw group during the gross pathological examination.”*

It is not clear what was the origin of the effects.

However, as this circumstance was already known at the time of the last approval at EU level and it was still concluded that 5-COOH-S-2200 is not toxicologically relevant [EFSA Journal 2015;13(5):4100], this is also supported for authorisation. However, this issue needs to be discussed at the latest during the next renewal phase of mandestrobin.

Based on DE comment provided during MSs consultation period:

The guidance document SANCO/221/2000 rev.11 has been revised and now requires aneugenicity to be covered (step 3, stage 2) for dossiers submitted after 1 May 2022. This data requirement is not met for the metabolite 5-COOH-S-2200. Appropriate data are required (e.g. *in vitro* MN assays performed according to OECD TG 487).

**This is a data gap.**

zRMS: However, 5-COOH-S-2200 is considered as non-genotoxic based on the results of the battery of tests undertaken with this metabolite: Ames test (negative), *In vitro* chromosomal aberration test (negative), *in vitro* mammalian gene mutation assay (negative) (according to EFSA Journal 2015;13(5):4100 and final addendum to the DAR, March 2015).

### 10.3.4 STEP 4: Exposure assessment – threshold of concern approach

The  $PEC_{gw}$  for 5-COOH-S-2200 was  $< 0.75 \mu\text{g/L}$ . There is no consumer exposure via other routes. 5-COOH-S-2200 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11.

### 10.3.5 STEP 5: Refined risk assessment

All  $PEC_{gw}$  values are  $<0.75 \mu\text{g/L}$ .

## 10.4 Relevance assessment of DX-CA-S-2200

The relevance of the groundwater metabolite DX-CA-S-2200 has not been assessed at EU level.

When considering the mitigation measures needed for mandestrobin to pass the risk assessment for groundwater contamination (application every other year on winter and summer oilseed rape, for soils with  $\text{pH CaCl}_2 < 7.2$ ), the maximum  $PEC_{gw}$  for DX-CA-S-2200 are below  $0.1 \mu\text{g/L}$ . Therefore a relevance assessment according to SANCO/221/2000 is not required.

Table 10.4-1: Summary of the relevance assessment for DX-CA-S-2200

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	No
Quantification of	STEP 2	Max $PEC_{gw}$	$< 0.1 \mu\text{g/L}$
			when considering application every other year



<b>ground-water con-tamina-tion</b>			Based on	All scenarios
<b>Hazard assess-ment</b>	STEP 3	Stage 1	Biological activity comparable to the parent?	Not performed.
		Stage 2	Genotoxic properties of metabolite	
		Stage 3	Toxic properties of metabolite;	
			Classification of parent	
			Classification of metabolite	
<b>Con-sumer health risk as-sess-ment</b>	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Not performed.
	STEP 5			Not performed.

#### 10.4.1 STEP 1: Exclusion of degradation products of no concern

DX-CA-S-2200 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

#### 10.4.2 STEP 2: Quantification of potential groundwater contamination

PEC<sub>gw</sub> calculations after leaching from soil for DX-CA-S-2200 were performed (see Part B, Section 8, chapter 8.8). PEC<sub>gw</sub> values are below 0.1 µg/L when considering the mitigation measures needed for parent mandestrobin. Details are given in Part B, Section 8, chapter 8.8.  
No further assessment is required.

#### 10.4.3 STEP 3: Hazard assessment – identification of relevant metabolites

Not performed.

#### 10.4.4 STEP 4: Exposure assessment – threshold of concern approach

Not performed.

#### 10.4.5 STEP 5: Refined risk assessment

Not performed.

## Appendix 1    Lists of data considered in support of the evaluation

### List of data submitted by the applicant and relied on

<b>Data point</b>	<b>Author(s)</b>	<b>Year</b>	<b>Title Company Report No. Source (where different from company) GLP or GEP status Published or not</b>	<b>Vertebrate study Y/N</b>	<b>Owner</b>