European Union Risk Management Plan
YUVANCI® (macitentan/tadalafil FDC)

Data lock point for current RMP	05 Feb 2023	Version number	1.3

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RMP Version Number: 1.3
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PPD

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	1.3
Rationale for submitting an updated RMP (if applicable)	Not applicable
Summary of significant changes in this RMP:	Not applicable

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted On**	**Procedure Number**
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	Not applicable
Approved within procedure	Not applicable
Date of approval (Competent authority opinion date)	Not applicable

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Macitentan/tadalafil FDC
Pharmacotherapeutic group(s) (ATC Code)	C02KX54
Marketing Authorization Applicant	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1 (macitentan/tadalafil FDC [YUVANCI])
Invented name(s) in the EEA	YUVANCI
Marketing authorization procedure	Centralized
Brief description of the product	*Chemical class* Macitentan is an orally active, non-peptide, potent dual ERA. Tadalafil is a potent and selective PDE-5 inhibitor.
	Summary of mode of action Macitentan is an orally active potent ERA, active on both ET_A and ET_B receptors, and approximately 100-fold more selective for ET_A as compared to ET_B in vitro. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents ET-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation. Inhibition of PDE-5 by tadalafil causes an increase in the concentrations of cGMP, resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.
	Important information about its composition The macitentan active substance is a sulfamide substituted pyrimidine of chemical origin. The tadalafil active substance is derived from chemical origin.
Reference to the Product Information	Mod1.3.1/SPC, Labelling and Package Leaflet
Indication(s) in the EEA	Current: YUVANCI is indicated as substitution therapy for the long-term treatment of PAH in adult patients of WHO FC II to III who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of YUVANCI is one 10 mg/40 mg tablet taken orally once daily.

	For patients who are currently treated with 10 mg macitentan and 40 mg tadalafil as separate tablets use YUVANCI 10 mg/40 mg tablet. For patients who are currently treated with 10 mg macitentan and 20 mg tadalafil as separate tablets use YUVANCI 10 mg/20 mg tablet. The dose may be increased to 10/40 mg once per day, based on tolerability.	
	Proposed: Not applicable	
Pharmaceutical form(s) and strengths	Current: *YUVANCI 10 mg/20 mg film-coated tablets:* Pink, oblong, 13 mm × 6 mm film-coated tablets debossed with "1020" on one side and "MT" on the other side. *YUVANCI 10 mg/40 mg film-coated tablets:* White to almost white, oblong, 15 mm × 7 mm film-coated tablets debossed with "1040" on one side and "MT" on the other side.	
	Proposed: Not applicable	
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1. Please refer to the approved macitentan and tadalafil EU RMPs for epidemiology information.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section focuses only on data generated for macitentan co-administered with tadalafil or M/T FDC. Please refer to the approved macitentan and tadalafil EU RMPs for more information.

Key Safety Findings	Relevance to Human Usage
Primary Pharmacodynamics	
Macitentan co-administered with tadalafil	
Macitentan co-administered with tadalafil had a synergistic effect in decreasing blood pressure in rat models of systemic hypertension and in decreasing mean pulmonary arterial pressure without increasing the risk of exaggerated systemic vasodilation in a rat model of pulmonary hypertension.	In clinical trials, hypotension has been reported with both M/T FDC and the loose combination of macitentan and tadalafil.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The development of M/T FDC is based primarily on Study AC-077A301 (A DUE), the pivotal Phase 3 study in participants with PAH designed to compare the efficacy and safety of macitentan (10 mg) and tadalafil (40 mg) monotherapies with M/T 10/40 mg FDC. Further support for the development of M/T FDC comes from Phase 1 bioequivalence studies in healthy volunteers (data not included in the RMP) and Phase 3/4 studies in which participants received a loose combination of macitentan and tadalafil.

Macitentan (marketed as OPSUMIT®) and tadalafil (marketed as ADCIRCA®) are established treatments for PAH approved in major markets with a well-established safety profile.

M/T FDC has been developed for the treatment of PAH.

This RMP includes data from the following clinical studies:

PAH clinical trial comparing macitentan (10 mg) and tadalafil (40 mg) monotherapies with M/T 10/40 mg FDC:

- AC-077A301 (A DUE; pivotal study): Ongoing, prospective, multicenter, DB, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 study to compare the efficacy and safety of macitentan (10 mg) and tadalafil (40 mg) monotherapies with the corresponding M/T 10/40 mg FDC in participants with PAH (either PAH-specific treatment-naïve or stable treatment with ERA or PDE-5i monotherapy), followed by an OL treatment period with M/T FDC. The Phase 3 study comprises 2 periods:
  - A completed, 16-week, prospective, multicenter, adaptive, triple-dummy, parallel-group, and group-sequential, randomized, DB period. For participants who were not on a therapeutic PDE-5i dose at baseline, a 1-week titration period of macitentan 10 mg and tadalafil 20 mg was applied.
  - An ongoing, single-arm, 24-month, OL treatment period in which all participants receive M/T 10/40 mg FDC, irrespective of DB treatment. Data up to a cut-off of 31 December 2022 are included in this RMP.

PAH clinical trial of loose combination of macitentan (10 mg) and tadalafil (40 mg) (macitentan and tadalafil were administered as study drugs):

- AC-065A308 (TRITON): Multicenter, DB, placebo-controlled, Phase 3b study evaluating the efficacy and safety of initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral combination therapy in participants with newly diagnosed PAH.
  - Participants treated with triple therapy (macitentan, tadalafil, and selexipag) were not included in the analysis as selexipag was administered as the investigational drug.

PAH clinical trials of loose combination of macitentan (10 mg) and tadalafil (where macitentan was the study drug and tadalafil was administered as a concomitant medication in some participants):

- AC-055-403 (REPAIR): Prospective, multicenter, single-arm, OL, Phase 4 study to evaluate the effects of macitentan on right ventricular remodeling in PAH by cardiac magnetic resonance imaging.
- AC-055-401/402 (SYMPHONY OL & Ext): Multicenter, OL, single-arm, Phase 3b study of macitentan in participants with PAH to psychometrically validate the PAH-SYMPACT® instrument and its OL, single-arm extension study.
- AC-055-310/311 (ORCHESTRA OL & Ext): Multicenter, OL, single-arm, Phase 3b study of macitentan in participants with PAH to psychometrically validate the PAH-SYMPACT® instrument and its OL, single-arm extension study.

Observational studies of PAH new users for macitentan in which a sub-cohort of PAH patients were treated with macitentan (10 mg) co-administered with tadalafil:

- AC-055-503 (OPUS): Multicenter, prospective, long-term, longitudinal, observational drug registry of new pulmonary hypertension users of OPSUMIT conducted in the US. OPUS registry was designed for a post-marketing requirement after macitentan launch in the US in 2013.
- AC-055-510 (OrPHeUS): Multicenter, retrospective medical chart review of OPSUMIT users who initiated OPSUMIT therapy for the first time in the US; this study was set up to complement the OPUS registry in order to fulfill the post-marketing requirement.

SIII.2. Clinical Trial Exposure

Exposure in the DB Period of Study AC-077A301 (A DUE)

Exposure to M/T FDC, macitentan, and tadalafil in the DB period of Study AC-077A301 (A DUE) is summarized for the RDB Safety Set (defined below) in Table SIII.1 through Table SIII.3 for all participants by duration, by age and sex, and by ethnicity.

The RDB Safety Set included all participants who received at least 1 dose of study treatment in the DB treatment period of the A DUE study. Participants were evaluated according to the study treatment received.

Table SIII.1 Exposure by Duration in Participants Treated with M/T FDC, Macitentan, and Tadalafil in the DB Period; RDB Safety Set (Study AC-077A301)

	M/T FDC N = 107		Macitentan N = 35		Tadalafil N = 44	
Duration of exposure	Participants	Participant-years	Participants	Participant-years	Participants	Participant-years
<1 m	10	0.4	0		0	
1 to <3 m	3	0.5	0		1	0.2
3 to <6 m	94	29.6	35	11.3	43	13.3
Total	107	30.4	35	11.3	44	13.5

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.
1 month = 30.4375 days.

Table SIII.2 Exposure by Age-group and Sex in Participants Treated with M/T FDC, Macitentan, and Tadalafil in the DB Period; RDB Safety Set (Study AC-077A301)

	M/T FDC N = 107			
Age group	Participants Male	Participants Female	Participant-years Male	Participant-years Female
<18 years	0	0		
18 to 64 years	19	68	6.0	19.2
65 to 74 years	4	8	1.3	2.2
75 to 84 years	2	6	0.4	1.3
>= 85 years	0	0		
Total	25	82	7.7	22.7

	Macitentan N = 35			
Age group	Participants Male	Participants Female	Participant-years Male	Participant-years Female
<18 years	0	0		
18 to 64 years	4	23	1.4	7.4
65 to 74 years	2	5	0.6	1.7
75 to 84 years	0	1		0.3
>= 85 years	0	0		
Total	6	29	2.0	9.3

	Tadalafil N = 44			
Age group	Participants Male	Participants Female	Participant-years Male	Participant-years Female
<18 years	0	0		
18 to 64 years	8	26	2.5	8.0
65 to 74 years	1	6	0.3	1.8
75 to 84 years	1	2	0.3	0.6
>= 85 years	0	0		
Total	10	34	3.1	10.4

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.

Table SIII.3 Exposure by Ethnic Origin in Participants Treated with M/T FDC, Macitentan, and Tadalafil in the DB Period; RDB Safety Set (Study AC-077A301)

	M/T FDC N = 107		Macitentan N = 35		Tadalafil N = 44	
Race/ethnicity	Participants	Participant-years	Participants	Participant-years	Participants	Participant-years
Caucasian/Hispanic	66	18.3	20	6.4	29	8.9
Asian	36	10.9	12	3.9	11	3.3
Black	2	0.3	1	0.3	2	0.6
Other	1	0.4	0		0	
Total	105	29.8	33	10.7	42	12.9
Missing	2		2		2	

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.
Participants with missing ethnic origin are not contributing to the total participant-years exposure.

Exposure in the Combined DB and OL Period of Study AC-077A301 (A DUE)

Exposure to M/T FDC in the combined DB and OL period of Study AC-077A301 (A DUE) is summarized for the Combination Safety Set (defined below) in Table SIII.4 through Table SIII.6 for all participants by duration, by age and sex, and by ethnicity. In the DB period, 186 participants (35 macitentan monotherapy, 44 tadalafil monotherapy, and 107 M/T FDC) received DB study treatment, 185 of whom received M/T FDC at any time in the DB and OL period. The DB period is completed and data from the OL period are as of 31 December 2022.

The Combination Safety Set included all participants randomized to M/T FDC in the DB period who received at least 1 dose of M/T FDC study treatment and all participants who received at least 1 dose of M/T FDC study treatment in the OL period, regardless of DB study treatment. For participants treated with M/T FDC study treatment in the DB period, data from both the DB and OL period were considered. For participants treated with monotherapy in the DB period, only data from the OL period were considered, except for baseline data, which may originate from the DB period. For participants randomized to monotherapy arms in the DB period, the start date of the macitentan and tadalafil combination was the date of the first dose of M/T FDC in the OL period.

Table SIII.4 Exposure by Duration in Participants Treated with M/T FDC in the DB/OL Period; Combination Safety Set (Study AC-077A301)

	DB/OL M/T FDC N = 185	
Duration of exposure	Participants	Participant-years
<1 m	12	0.4
1 to <3 m	6	0.9
3 to <6 m	18	7.2
6 to <12 m	46	34.7
12 to <24 m	74	114.9

Table SIII.4 Exposure by Duration in Participants Treated with M/T FDC in the DB/OL Period; Combination Safety Set (Study AC-077A301)

	DB/OL M/T FDC N = 185	
Duration of exposure	Participants	Participant-years
24 to <36 m	29	65.8
Total	185	224.0

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.
1 month = 30.4375 days.

Table SIII.5 Exposure by Age-group and Sex in Participants Treated with M/T FDC in the DB/OL period; Combination Safety Set (Study AC-077A301)

	DB/OL M/T FDC N = 185			
Age group	Participants Male	Participants Female	Participant-years Male	Participant-years Female
<18 years	0	0		
18 to 64 years	31	116	38.2	140.6
65 to 74 years	7	19	10.6	23.3
75 to 84 years	3	9	2.3	9.0
>= 85 years	0	0		
Total	41	144	51.2	172.8

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.

Table SIII.6 Exposure by Ethnic Origin in Participants Treated with M/T FDC in the DB/OL period; Combination Safety Set (Study AC-077A301)

	DB/OL M/T FDC N = 185	
Race/ethnicity	Participants	Participant-years
Caucasian/Hispanic	115	144.2
Asian	58	68.7
Black	5	2.9
Other	1	1.1
Total	179	216.9
Missing	6	

M/T FDC = Macitentan/tadalafil fixed dose combination.
Exposure includes treatment interruptions.
Participants with missing ethnic origin are not contributing to the total participant-years exposure.

Exposure to Macitentan 10 mg + Tadalafil (Combined Analysis of Data from Studies AC-065A308 [TRITON]), AC-055-403 [REPAIR], AC-055-401/402 [SYMPHONY OL & Ext], and AC-055-310/311 [ORCHESTRA OL & Ext])

The Safety Set for Studies AC-065A308 (TRITON), AC-055-403 (REPAIR), AC-055-401/402 (SYMPHONY OL & Ext), and AC-055-310/311 (ORCHESTRA OL & Ext) includes all participants who received macitentan 10 mg and tadalafil (any dose) as a study treatment or as a concomitant medication. For TRITON, only participants in the double therapy group (macitentan, tadalafil, and placebo) are included. Participants in the triple therapy group (macitentan, tadalafil, and selexipag) are excluded as selexipag was administered as the investigational drug.

Exposure to macitentan 10 mg and tadalafil (loose combination) in the Safety Set is summarized in Table SIII.7 through Table SIII.9 for all participants by duration, by age and sex, and by ethnicity. This dataset comprised 127 participants from TRITON, 30 from REPAIR, 73 from SYMPHONY (OL & Ext), and 36 from ORCHESTRA (OL & Ext).

Table SIII.7 Exposure by Duration in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; Safety Set (Loose Combination of Macitentan and Tadalafil) (Studies AC-065A308 [TRITON, M+T arm], AC-055-403 [REPAIR], AC-055-401/402 [SYMPHONY OL & Ext], AC-055-310/311 [ORCHESTRA OL & Ext])

	M/T loose combination N = 266	
Duration of exposure	Participants	Participant-years
<1 m	22	0.7
1 to <3 m	14	2.5
3 to <6 m	70	22.1
6 to <12 m	25	22.3
12 to <24 m	80	113.4
24 to <36 m	34	83.9
36 to <48 m	20	65.4
48 to <60 m	1	4.0
Total	266	314.4

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.
1 month = 30.4375 days.

Table SIII.8 Exposure by Age-group and Sex in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; Safety Set (Loose Combination of Macitentan and Tadalafil) (Studies AC-065A308 [TRITON, M+T arm], AC-055-403 [REPAIR], AC-055-401/402 [SYMPHONY OL & Ext], AC-055-310/311 [ORCHESTRA OL & Ext])

	M/T loose combination N = 266			
Age group	Participants Male	Participants Female	Participant-years Male	Participant-years Female
<18 years	0	0		
18 to 64 years	48	152	64.4	181.5
65 to 74 years	16	38	12.1	49.6
75 to 84 years	5	7	2.6	4.3
>= 85 years	0	0		
Total	69	197	79.0	235.4

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.

Table SIII.9 Exposure by Ethnic Origin in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; Safety Set (Loose Combination of Macitentan and Tadalafil) (Studies AC-065A308 [TRITON, M+T arm], AC-055-403 [REPAIR], AC-055-401/402 [SYMPHONY OL & Ext], AC-055-310/311 [ORCHESTRA OL & Ext])

	M/T loose combination N = 266	
Race/ethnicity	Participants	Participant-years
Caucasian/Hispanic	225	267.1
Asian	7	7.1
Black	10	12.7
Other	10	8.2
Total	252	295.1
Missing	14	

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.
Participants with missing ethnic origin are not contributing to the total participant-years exposure.

Exposure in the Cohort of PAH Patients Receiving Loose Combination of Macitentan and Tadalafil from the OPUS and OrPHeUS Observational Studies

The PAH set (loose combination of macitentan and tadalafil) includes all patients who received loose combination of macitentan and tadalafil in either of the following 2 studies:

- AC-055-510 (OrPHeUS)
- AC-055-503 (OPUS)

Exposure to macitentan and tadalafil in the PAH set (loose combination of macitentan and tadalafil) is summarized in Table SIII.10 through Table SIII.12 for all patients by duration, by age and sex, and by ethnicity.

Table SIII.10 Exposure by Duration in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; PAH Set with Loose Combination of Macitentan and Tadalafil (Studies AC-055-503 [OPUS], AC-055-510 [OrPHeUS])

	M/T loose combination (OPUS) N = 604		M/T loose combination (OrPHeUS) N = 732		M/T loose combination (OPUS+OrPHeUS) N = 1336	
Duration of exposure	Participants	Participant-years	Participants	Participant-years	Participants	Participant-years
<1 m	71	2.9	50	2.2	121	5.1
1 to <3 m	78	11.5	74	11.3	152	22.9
3 to <6 m	44	16.0	87	32.6	131	48.6
6 to <12 m	82	63.0	110	82.1	192	145.1
12 to <24 m	116	169.6	211	313.7	327	483.3
24 to <36 m	84	207.3	147	358.5	231	565.8
36 to <48 m	67	236.4	53	169.0	120	405.3
48 to <60 m	50	224.5	0	.	50	224.5
60 to <72 m	12	62.8	0	.	12	62.8
Total	604	994.0	732	969.4	1336	1963.4

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.
1 month = 30.4375 days.

Table SIII.11 Exposure by Age-group and Sex in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; PAH Set with Loose Combination of Macitentan and Tadalafil (Studies AC-055-503 [OPUS], AC-055-510 [OrPHeUS])

	M/T loose combination (OPUS) N = 604				M/T loose combination (OrPHeUS) N = 732				M/T loose combination (OPUS+OrPHeUS) N = 1336			
	Participants		Participant-years		Participants		Participant-years		Participants		Participant-years	
Age group	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<18 years	2	0	4.3		0	1		0.5	2	1	4.3	0.5
18 to 64 years	84	286	137.7	496.9	103	351	139.2	490.5	187	637	276.8	987.4
65 to 74 years	38	117	65.1	175.4	50	132	54.8	170.4	88	249	119.9	345.8
75 to 84 years	18	47	39.5	60.0	21	65	25.9	79.1	39	112	65.4	139.1
>= 85 years	4	8	1.7	13.5	1	8	1.6	7.4	5	16	3.2	20.9
Total	146	458	248.2	745.7	175	557	221.5	747.9	321	1015	469.7	1493.7

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.

Table SIII.12 Exposure by Ethnic Origin in Participants Treated with Loose Combination of Macitentan 10 mg and Tadalafil; PAH Set with Loose Combination of Macitentan and Tadalafil (Studies AC-055-503 [OPUS], AC-055-510 [OrPHeUS])

	M/T loose combination (OPUS) N = 604		M/T loose combination (OrPHeUS) N = 732		M/T loose combination (OPUS+OrPHeUS) N = 1336	
Race/ethnicity	Participants	Participant-years	Participants	Participant-years	Participants	Participant-years
Caucasian/Hispanic	469	756.3	543	727.9	1012	1484.2
Black	92	166.4	117	146.5	209	312.9
Other	42	69.3	61	80.0	103	149.3
Total	603	991.9	721	954.4	1324	1946.3
Missing	1		11		12	

M/T = Macitentan/Tadalafil.
Exposure includes treatment interruptions.
Participants with missing ethnic origin are not contributing to the total participant-years exposure.

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1. Please refer to the approved macitentan and tadalafil EU RMPs for more information.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1. Information on cumulative postauthorization exposure will be presented in the EU PBRER for M/T FDC.

SV.1. Postauthorization Exposure

Not applicable.

SV.1.1. Method used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1. Please refer to the approved macitentan and tadalafil EU RMPs for more information.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

M/T FDC is a fixed dose combination that does not contain a new active substance. No new safety concerns have been identified specifically for M/T FDC based on Study AC-077A301/A DUE. The important identified and potential risks for M/T FDC were identified based on the known safety concerns of the separate components (macitentan and tadalafil).

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

M/T FDC is a fixed dose combination that does not contain a new active substance. As there are approved EU RMPs for the separate components (macitentan and tadalafil), this section is not required per GVP Module V, Revision 2, Section V.C.1.1.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important Identified Risks:

1. Hepatotoxicity
2. Teratogenicity

Important Potential Risks:

None.

Missing Information:

None.

The list of important identified and important potential risks for M/T FDC reflects the known safety concerns of both macitentan and tadalafil.

The important identified risks are summarized for A DUE (DB period), combined data from the A DUE DB and OL periods, combined data from TRITON (M+T arm), REPAIR, SYMPHONY OL & Ext, and ORCHESTRA OL & Ext, as well as separately for the OPUS and OrPHeUS studies.

For OPUS (OPSUMIT Users Registry), severity of AEs and the reasons for tadalafil discontinuation were not collected. Therefore, AEs leading to discontinuation of treatment and AEs by severity could not be summarized. For OrPHeUS (OPSUMIT retrospective medical chart review), only data on hepatic AEs were collected.

Adverse events were coded using MedDRA Version 25.0 for the supportive clinical trials and observational studies. For the A DUE DB and OL periods, the latest MedDRA version was used (Version 25.1).

The background information for tadalafil is adapted from the tadalafil EU RMP (Version 8.2, December 2016).

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Hepatotoxicity

Potential Mechanisms:

The mechanisms of liver toxicity with other ERAs are not fully elucidated. For bosentan, BSEP blockage and/or direct hepatotoxic effect have been implicated.

Macitentan is an alkyl-sulfamide with a pyrimidine scaffold containing 3 aromatic rings. It contains no substructures considered to be toxicophores for liver toxicity. The chemical nature of human metabolites and the cytochrome P450 enzymes involved in its metabolism do not indicate any liver liability. The 2 macitentan metabolites circulating in human plasma, aprocitentan and ACT-373898, were fully characterized in the nonclinical safety program.

Macitentan and the pharmacologically active metabolite aprocitentan do not inhibit the major human transport proteins responsible for hepatic bile salt transport, ie, BSEP and sodium dependent taurocholate co-transporting polypeptide, at clinically relevant concentrations. Macitentan has no effect on serum bile salt concentrations in animals up to very high dose levels and during chronic dosing or in healthy human participants at high single doses or supratherapeutic doses for up to 10 days.

The nonclinical profile of macitentan does not indicate a relevant risk for liver toxicity in humans.

Evidence Source(s) and Strength of Evidence:

Macitentan, like other medicines of the same class, may affect the liver.

The mechanism of this adverse impact is unclear. Interruption or stopping treatment may be necessary.

There are no data to support a risk for liver toxicity associated with tadalafil.

Characterization of the Risk:

Table SVII.1 Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Events of Special Interest in the DB Period; RDB Safety Set (Study AC-077A301)

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: RDB Safety Set	70	35	86	44	107
Hepatotoxicity					
Participants with at least one AE	0	1 (2.9%)	1 (1.2%)	4 (9.1%)	1 (0.9%)
Relative Risk 95% confidence interval	NE		0.128 (0.015 - 1.110)		
Participants at least one AE with:					
Serious	0	0	0	0	0
Leading to discontinuation of treatment	0	0	1 (1.2%)	1 (2.3%)	1 (0.9%)
Fatal outcome	0	0	0	0	0
Number of AEs (including recurrences)	0	3	1	5	1
Participant-years exposure	19.29	11.31	24.59	13.48	30.45
Average annualized event rate	0.0000	0.2652	0.0407	0.3710	0.0328
Severity (worst)*					
Mild	0	1 (2.9%)	0	3 (6.8%)	0
Moderate	0	0	0	1 (2.3%)	0
Severe	0	0	1 (1.2%)	0	1 (0.9%)

M/T FDC = Macitentan/tadalafil fixed dose combination.
* The event experienced by the participant with the worst severity is used.
Adverse events are coded using MedDRA Version 25.1.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min (EOT-DB+30 days, start date of open-label treatment).
NE = Non-estimable.

Table SVII.2 Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Events of Special Interest in the DB/OL Period; Combination Safety Set (Study AC-077A301)

	DB/OL M/T FDC
Analysis set: Combination Safety Set	185
Hepatotoxicity	
Participants with at least one AE	9 (4.9%)
Participants at least one AE with:	
Serious	1 (0.5%)
Leading to discontinuation of treatment	4 (2.2%)
Fatal outcome	0
Number of AEs (including recurrences)	21
Participant-years exposure	224.00
Average annualized event rate	0.0938
Severity (worst)*	
Mild	5 (2.7%)
Moderate	3 (1.6%)
Severe	1 (0.5%)

* The event experienced by the participant with the worst severity is used.
Adverse events are coded using MedDRA Version 25.1.
M/T FDC = Macitentan/tadalafil fixed dose combination.
Note: The combination treatment-emergent period is defined from first intake of macitentan 10 mg and tadalafil (20 mg or 40 mg) in DB or OL treatment period up to EOT (EOT-DB or EOT-OL) + 30 days.

Table SVII.3 Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Events of Special Interest; Safety Set (Loose Combination of Macitentan and Tadalafil) (Studies AC-065A308 [TRITON, M+T arm], AC-055-403 [REPAIR], AC-055-401/402 [SYMPHONY OL & Ext], AC-055-310/311 [ORCHESTRA OL & Ext])

	M/T loose combination
Analysis set: Safety Set (Loose Combination of Macitentan and Tadalafil)	266
Hepatotoxicity	
Participants with at least one AE	19 (7.1%)
Participants at least one AE with:	
Serious	2 (0.8%)
Leading to discontinuation of treatment	1 (0.4%)
Fatal outcome	0
Number of AEs (including recurrences)	25
Participant-years exposure	314.41
Average annualized event rate	0.0795
Severity (worst)*	
Mild	10 (3.8%)
Moderate	6 (2.3%)
Severe	3 (1.1%)

* The event experienced by the participant with the worst severity is used.
Adverse events are coded using MedDRA Version 25.0.
M/T = Macitentan/Tadalafil.
Note: The combination treatment-emergent period is defined from first intake of macitentan 10 mg and tadalafil (20 mg or 40 mg) in DB or OL treatment period up to EOT (EOT-DB or EOT-OL) + 30 days.

Table SVII.4 Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Events of Special Interest; PAH Set with Loose Combination of Macitentan and Tadalafil (Study AC-055-503 [OPUS])

	M/T loose combination
Analysis set: PAH set with loose combination of macitentan and tadalafil	604
Hepatotoxicity	
Participants with at least one AE	50 (8.3%)
Participants at least one AE with:	
Serious	0
Fatal outcome	4 (0.7%)
Number of AEs (including recurrences)	97
Participant-years exposure	993.97
Average annualized event rate	0.0976

Adverse events are coded using MedDRA Version 25.0.
M/T = Macitentan/Tadalafil.
Note: Treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

Table SVII.5 Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Events of Special Interest; PAH Set with Loose Combination of Macitentan and Tadalafil (Study AC-055-510 [OrPHeUS])

	M/T loose combination
Analysis set: PAH set with loose combination of macitentan and tadalafil	732
Hepatotoxicity	
Participants with at least one AE	20 (2.7%)
Participants at least one AE with:	
Fatal outcome	0
Participant-years exposure	969.39

Adverse events are coded using MedDRA Version 25.0.
M/T = Macitentan/Tadalafil.
Note: Treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

Relevant Data from Study AC-077A301 (A DUE)

A DUE DB Period:

Hepatic AESI were infrequently reported across all treatment groups during the DB period. No imbalance in incidence of markedly abnormal AST and/or ALT was observed between treatment groups and no participant met the criteria for potential Hy's law (ie, ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN) during the DB period. No new safety concern was identified in participants receiving M/T FDC during the DB period.

In the M/T FDC group, 1 prior PDE-5i participant with a medical history of PPD experienced increased transaminases (ALT 18.8×ULN and AST 7.5×ULN). Total bilirubin remained normal. Study treatment was discontinued. The event resolved approximately 2 months later.

A DUE DB and OL Period:

In the A DUE DB and OL period up to the data cut-off date (N=185), the exposure-adjusted incidence rate of hepatic AESI was 4.08 events per 100 participant-years.

Of the 107 participants who received DB M/T FDC during the combined DB and OL period, 6 (5.6%) had a hepatic AESI, of which 1 was reported in the DB period (described above). Five participants had hepatic events only during the OL period, all of which were mild or moderate in intensity. These events were:

- Drug-induced hepatitis (ALT/AST >3×ULN on Day 148; highest elevation observed on Day 155 of ALT 8.6×ULN and AST 6.2×ULN; total bilirubin and ALP remained within normal limits). Study treatment was discontinued. The event of drug-induced hepatitis resolved;
- ALT, AST, ALP, bilirubin increased, and ocular icterus (relevant medical history of PPD ; this

participant had ALT <3×ULN and AST 5.8×ULN, with total bilirubin 1.2×ULN. More than 30 days after treatment discontinuation, total bilirubin increased to 2.6×ULN, with AST 4.3×ULN and ALT <2×ULN). The events of elevated ALP and ocular icterus resolved;

- Hepatic cirrhosis (assessed as related to hepatic congestion; ALT and AST were normal throughout treatment with M/T FDC), portal hypertension, and varices esophageal (outcome reported as death due to right ventricular failure; relevant medical history included PP prior episodes of right ventricular failure);
- Hepatic steatosis and hepatitis B (no action taken with study treatment; outcome reported as resolving for hepatitis B and ongoing at time of data cut-off for hepatic steatosis);
- Transaminase increased (ALT 1.9×ULN and AST 3.0×ULN; no action taken with study treatment; event ongoing at time of data cut-off).

Of the 78 participants who switched from DB monotherapy to OL M/T FDC, hepatic AESI were reported in 3 participants and were all mild in intensity. These events were varices esophageal and hepatitis B flare (DB-macitentan group; study treatment was discontinued and both events resolved); hepatitis B antibody abnormal (DB-tadalafil group; no action taken with study treatment; event ongoing at data cut-off); and ALT increased, AST increased, and hepatitis C (DB-tadalafil group; no action taken with study treatment; all events resolved).

Laboratory Data:

A DUE DB Period

In the A DUE 16-week DB period, there was 1 participant in the M/T FDC group, 2 participants in the tadalafil group, and none in the macitentan group with markedly abnormal AST and/or ALT values (Table SVII.6). The participant reported as experiencing ALT or AST ≥8×ULN is described in more detail above (see A DUE DB period). No participants met the criteria for potential Hy's law.

Table SVII.6 Treatment-emergent Liver Abnormalities by Treatment Group; Safety Set (A DUE 16-week DB Period)

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
ALT (U/L) or AST (U/L)					
N	35	63	44	82	100
ALT or AST >= 3 x ULN	0	0	2 (4.5%)	1 (1.2%)	1 (1.0%)
ALT or AST >= 5 x ULN	0	0	1 (2.3%)	1 (1.2%)	1 (1.0%)
ALT or AST >= 8 x ULN	0	0	0	1 (1.2%)	1 (1.0%)
ALT (U/L) or AST (U/L) and BILI (umol/L)[a]					
N	35	63	44	82	100
ALT or AST >= 3xULN and BILI >= 2xULN[b]	0	0	0	0	0

Key: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BILI = Bilirubin; ULN = Upper limit of normal; EOT-DB = End of treatment in double-blind treatment period.

[a] Blood sample for ALT or AST and bilirubin collected on the same day.

[b] ALT or AST and concomitant bilirubin increased compared to baseline.

Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min (EOT-DB+30 days, start date of open-label treatment).

Note: N is the number of subjects with at least 1 postbaseline value for the specified lab tests. Subject is counted in all categories which satisfied the abnormality criteria.

Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

A DUE DB and OL Period:

Of the participants treated with M/T FDC at any time during the A DUE DB and OL period with available laboratory data up to the data cut-off (N=178), 2/178 (1.1%) had ALT or AST ≥8×ULN (1 reported in the DB period), 2/178 (1.1%) had ALT or AST between 5× to 8×ULN (both during the OL period), and 2/178 (1.1%) had ALT and/or AST between 3× to 5×ULN (both during the OL period) (Table SVII.7). No participants met the criteria for potential Hy's law.

Table SVII.7 Number and Percentage of Participants With Treatment-emergent Liver Abnormalities in the Combined DB and OL Period; Combination Safety Set (Study AC-077A301) (Cut-off Date: 31DEC2022)

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Alanine Aminotransferase (U/L)[a]				
N	35	43	100	178
ALT >= 3 x ULN	1 (2.9%)	0	3 (3.0%)	4 (2.2%)
ALT >= 5 x ULN	1 (2.9%)	0	2 (2.0%)	3 (1.7%)
ALT >= 8 x ULN	0	0	2 (2.0%)	2 (1.1%)
Aspartate Aminotransferase (U/L)[a]				
N	35	43	100	178
AST >= 3 x ULN	1 (2.9%)	0	4 (4.0%)	5 (2.8%)
AST >= 5 x ULN	1 (2.9%)	0	3 (3.0%)	4 (2.2%)
AST >= 8 x ULN	0	0	0	0
ALT (U/L) and/or AST (U/L)[a]				
N	35	43	100	178
ALT and/or AST >= 3 x ULN	1 (2.9%)	0	5 (5.0%)	6 (3.4%)
ALT and/or AST >= 5 x ULN	1 (2.9%)	0	3 (3.0%)	4 (2.2%)
ALT and/or AST >= 8 x ULN	0	0	2 (2.0%)	2 (1.1%)
ALT (U/L) and/or AST (U/L)[b]				
N	35	43	100	178
ALT and/or AST >= 3 x ULN and <5 x ULN	0	0	2 (2.0%)	2 (1.1%)
ALT and/or AST >= 5 x ULN and <8 x ULN	1 (2.9%)	0	1 (1.0%)	2 (1.1%)
ALT and/or AST >= 8 x ULN	0	0	2 (2.0%)	2 (1.1%)
ALT (U/L) and/or AST (U/L) and BILI (umol/L)				
N	35	37	100	172
ALT and/or AST >= 3xULN and BILI >= 2xULN at the same time[c d]	0	0	0	0
ALT and/or AST >= 3xULN and BILI >= 2xULN at any time[d]	0	0	0	0

[a] Subject is counted in all categories which satisfied the marked abnormality criteria.
[b] These categories are mutually exclusive, a subject is counted once according to the highest treatment-emergent result.
[c] ALT or AST collected on the same day as bilirubin.
[d] ALT or AST and bilirubin increased compared to baseline.
Note: Under treatment period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. Under treatment period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (ie, covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: N is the number of subjects with at least 1 postbaseline value for the specified lab tests. Subject is counted in all categories which satisfied the marked abnormality criteria.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs used to characterize the risk of hepatotoxicity.

Risk Factors and Risk Groups:

Unknown in patients with severe hepatic impairment and ALT/AST >1.5×ULN as they were excluded from Study AC-077A301 (A DUE). Patients with ALT/AST >3×ULN at baseline or with moderate or severe liver impairment are excluded from clinical trials with macitentan.

Preventability:

M/T FDC is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or elevated baseline values of hepatic aminotransferases (AST and/or ALT >3×ULN).

Liver enzyme tests should be obtained prior to initiation of M/T FDC. Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended.

If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical symptoms of liver injury (eg, jaundice), M/T FDC treatment should be discontinued. Reinitiation of M/T FDC may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended.

Patients are instructed to talk to their doctor before they take M/T FDC if they have a severe liver problem.

Patients are informed that their doctor will carry out laboratory tests to test whether their liver is working properly prior to initiation and during treatment, as needed, with M/T FDC.

Patients are instructed not to take M/T FDC and to speak to their doctor if they have liver disease or if they have very high levels of liver enzymes in their blood. Patients are also advised to speak to their doctor immediately if they notice signs of liver impairment.

Impact on the Risk-benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Hepatic enzyme levels are measurable and monitorable. In severe cases, elevations of liver aminotransferases or other liver impairment events may require hospitalization.

Important Identified Risk: Teratogenicity

Potential Mechanisms:

The ET_A receptor pathway is critical to normal induction, migration, and maintenance of neural crest cells during early embryonic development. Disruption of this pathway, such as by ERA therapy, can lead to severe defects in neural crest derivatives and physical malformation (de Raaf 2015).

Evidence Source(s) and Strength of Evidence:

According to results from animal studies, macitentan and medicines of the same class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed.

Characterization of the Risk:

Macitentan/Tadalafil FDC

One participant became pregnant while on M/T FDC during the A DUE OL period leading to discontinuation of study treatment (last dose on Day 278) due to pregnancy. The participant underwent elective PPD and PPD on Day PPD and discontinued from the study on Day PPD.

Macitentan

Pregnancy was an exclusion criterion in macitentan clinical trials.

Cumulatively, up to 05 February 2023, 163 reports pertaining to female patients treated with macitentan during pregnancy have been received, including 25 cases from interventional clinical trials. A further 6 reports described paternal exposure to macitentan.

Of the 35 live births reported (3 from clinical trials, 8 from solicited programs, and 24 spontaneous reports [including 7 literature reports]), 1 clinical trial case described a premature baby born at 24 weeks' gestation who suffered complications of extreme prematurity (neonatal respiratory distress syndrome, sepsis, intracranial hemorrhage, and skin atrophy) and died 3 days after birth due to persistent hypotension.

No cases of congenital anomalies were reported during the macitentan clinical development program. No fetal malformations were reported in cases where the pregnancy outcome was induced or spontaneous abortion.

Cumulatively, 2 cases describing congenital anomalies have been received from all data sources:

- 1 case, referring to a premature baby with PPD on PPD PPD, diagnosed as PPD, was confounded by the mother's underlying SLE disease and concomitant medications;
- 1 case referred to a premature baby with PPD PPD

Based on the medical assessment of both cases, there was no evidence of a contributory role of macitentan and neither anomaly corresponded to the pattern of malformations that may be expected from ERAs based on nonclinical findings (ie, defects in neural crest derivatives).

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs used to characterize the risk of teratogenicity.

Risk Factors and Risk Groups:

All women of childbearing potential on M/T FDC therapy who are not using a reliable method of contraception.

Preventability:

M/T FDC is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception due to teratogenicity identified in the animal studies with macitentan.

M/T FDC treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. Women should not become pregnant for 1 month after discontinuation of M/T FDC. Monthly pregnancy tests during treatment with M/T FDC are recommended to allow for the early detection of pregnancy.

Patients are instructed to use a reliable form of birth control (contraception) whilst taking M/T FDC and to not take M/T FDC if they are pregnant, planning to become pregnant, or could become pregnant because they are not using reliable birth control. Patients are instructed to consult their doctor immediately if they become pregnant or think they may be pregnant while taking M/T FDC or shortly after stopping M/T FDC (up to 1 month).

Impact on the Risk-benefit Balance of the Product:

Pregnancy is strongly contraindicated for women with PAH, regardless of the medications used. The additional risk of teratogenicity from macitentan does not have a medically relevant impact on the benefit-risk balance of M/T FDC.

Public Health Impact:

Potential congenital abnormalities.

Important Potential Risks: None.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1 Summary of Safety Concerns

Important Identified Risks	Hepatotoxicity
	Teratogenicity
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

Routine pharmacovigilance activities conducted for all products, including M/T FDC, include the collection, follow-up, assessment, and reporting of individual case safety reports from any source; signal detection and evaluation to identify new risks; and preparation and submission of aggregate safety reports, such as Development Safety Update Reports and PBRERs.

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Teratogenicity	Each pregnancy is followed up to final outcome. Pregnancy information (including maternal and baby information) is collected using the Macitentan-Tadalafil FDC Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-16843). Closely monitor compliance with the labeling pregnancy contraindication and further characterize the risk if reported.

Other Forms of Routine Pharmacovigilance Activities

Not applicable.

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Hepatotoxicity	**Routine risk communication:** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you take Yuvanci). PL Section 4 (Possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Warning that M/T FDC is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or elevated baseline values of aminotransferases (AST and/or ALT >3×ULN) is given in SmPC Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), and 4.4 (Special warnings and precautions for use). Recommendation that liver enzyme tests be obtained prior to initiation of M/T FDC and repeated monthly during treatment is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation that patients should be monitored for signs of hepatic injury is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation to discontinue M/T FDC if sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical symptoms of liver injury is given in SmPC Section 4.4 (Special warnings and precautions for use). This section also notes that reinitiation of M/T FDC may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury; the advice of a hepatologist is recommended. Warning to patients not to take M/T FDC and to speak to their doctor if they have liver disease or if they have very high levels of liver enzymes in their blood is provided in PL Section 2 (What you need to know before you take Yuvanci). Patients are informed that their doctor will carry out laboratory tests to test whether their liver is working properly prior to initiation and during treatment, as needed, with M/T FDC in PL Section 2 (What you need to know before you take Yuvanci). Recommendation for patients to speak to their doctor immediately if they notice signs of liver impairment is given in PL Section 2 (What you need to

Safety Concern	Routine Risk Minimization Activities
	know before you take Yuvanci). This section also contains a recommendation for patients to speak to their doctor if they have a severe liver problem before taking M/T FDC. **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Teratogenicity	**Routine risk communication:** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction). SmPC Section 4.6 (Fertility, pregnancy and lactation). SmPC Section 5.3 (Preclinical safety data). PL Section 2 (What you need to know before you take Yuvanci). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Warning that use of M/T FDC is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception due to teratogenicity identified in animal studies with macitentan is given in SmPC Section 4.6 (Fertility, pregnancy and lactation). Appropriate text is also given in SmPC Section 4.3 (Contraindications). Recommendation that M/T FDC treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation that women should not become pregnant for 1 month after discontinuation of M/T FDC is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation for use of monthly pregnancy tests during treatment with M/T FDC to allow for early detection of pregnancy is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendations for patients to use a reliable form of birth control (contraception) whilst taking M/T FDC and to not take M/T FDC if they are pregnant, are planning to become pregnant, or could be pregnant because they are not using reliable birth control are given in PL Section 2 (What you need to know before you take Yuvanci). Warning that treatment with M/T FDC must not be taken during pregnancy is provided in PL Section 2 (What you need to know before you take Yuvanci). This section contains recommendations for patients to consult their doctor immediately if they become pregnant or think they may be pregnant while taking M/T FDC or shortly after stopping M/T FDC (up to 1 month). Recommendations for patients to have a pregnancy test before initiation of M/T FDC and every month during treatment are given in PL Section 2 (What you

Safety Concern	Routine Risk Minimization Activities
	need to know before you take Yuvanci). **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimization Measures

Educational Tools (Patient Card)

Educational Tools (Patient Card)	
Objective(s):	This additional risk minimization activity aims: • To educate patients about the risks associated with M/T FDC, with an emphasis on hepatotoxicity and teratogenicity. • To inform patients where to obtain more information about their treatment. • To educate patients on the need to report immediately to their prescribing physician any pregnancy that may occur, as well as symptoms and signs of any potential adverse drug reactions associated with hepatotoxicity.
Rationale for the additional risk minimization activity:	These efforts reinforce patient knowledge regarding the safe use of M/T FDC, thereby mitigating the risks associated with M/T FDC treatment.
Target audience and planned distribution path:	The Patient Card is provided as part of the product packaging.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Reporting trend analyses from post-marketing safety data are monitored in the PBRER/PSUR. Assessments are done at the end of each PBRER/PSUR reporting interval, starting 12 to 18 months following EU approval, and in time for a renewal of a marketing authorization. Stable reporting trend analysis from post-marketing safety data is the criterion for success.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you take Yuvanci). PL Section 4 (Possible side effects). Warning that M/T FDC is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or elevated baseline values of aminotransferases (AST and/or ALT >3×ULN) is given in SmPC Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), and 4.4 (Special warnings and precautions for use). Recommendation that liver enzyme tests be obtained prior to initiation of M/T FDC and repeated monthly during treatment is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation that patients should be monitored for signs of hepatic injury is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation to discontinue M/T FDC if sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical symptoms of liver injury is given in SmPC Section 4.4 (Special warnings and precautions for use). This section	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	also notes that reinitiation of M/T FDC may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury; the advice of a hepatologist is recommended. Warning to patients not to take M/T FDC and to speak to their doctor if they have liver disease or if they have very high levels of liver enzymes in their blood is provided in PL Section 2 (What you need to know before you take Yuvanci). Patients are informed that their doctor will carry out laboratory tests to test whether their liver is working properly prior to initiation and during treatment, as needed, with M/T FDC in PL Section 2 (What you need to know before you take Yuvanci). Recommendation for patients to speak to their doctor immediately if they notice signs of liver impairment is given in PL Section 2 (What you need to know before you take Yuvanci). This section also contains a recommendation for patients to speak to their doctor if they have a severe liver problem before taking M/T FDC. Legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.	
Teratogenicity	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction). SmPC Section 4.6 (Fertility, pregnancy and lactation). SmPC Section 5.3 (Preclinical safety	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Macitentan-Tadalafil FDC Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-16843). **Additional pharmacovigilance activities:** None.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	data). PL Section 2 (What you need to know before you take Yuvanci). Warning that use of M/T FDC is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception due to teratogenicity identified in animal studies with macitentan is given in SmPC Section 4.6 (Fertility, pregnancy and lactation). Appropriate text is also given in SmPC Section 4.3 (Contraindications). Recommendation that M/T FDC treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation that women should not become pregnant for 1 month after discontinuation of M/T FDC is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation for use of monthly pregnancy tests during treatment with M/T FDC to allow for early detection of pregnancy is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendations for patients to use a reliable form of birth control (contraception) whilst taking M/T FDC and to not take M/T FDC if they are pregnant, are planning to become pregnant, or could be pregnant because they are not using reliable birth control are given in PL Section 2 (What you need to know before you take Yuvanci). Warning that treatment with M/T FDC must not be taken during pregnancy is	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	provided in PL Section 2 (What you need to know before you take Yuvanci). This section contains recommendations for patients to consult their doctor immediately if they become pregnant or think they may be pregnant while taking M/T FDC or shortly after stopping M/T FDC (up to 1 month). Recommendations for patients to have a pregnancy test before initiation of M/T FDC and every month during treatment are given in PL Section 2 (What you need to know before you take Yuvanci). Legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.	

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for YUVANCI (Macitentan/Tadaladil Fixed Dose Combination)

This is a summary of the risk management plan (RMP) for YUVANCI. The RMP details important risks of YUVANCI, how these risks can be minimized, and how more information will be obtained about YUVANCI's risks and uncertainties (missing information).

YUVANCI 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how YUVANCI should be used.

This summary of the RMP for YUVANCI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of YUVANCI's RMP.

I. The Medicine and What it is Used For

YUVANCI is authorized as substitution therapy for the treatment of pulmonary arterial hypertension (PAH) in adult patients who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets; see SmPC for the full indication. It contains macitentan and tadalafil as the active substances and is taken orally as 1 tablet.

Further information about the evaluation of YUVANCI's benefits can be found in YUVANCI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/yuvanci

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

- Important risks of YUVANCI, together with measures to minimize such risks, are outlined below.
- Measures to minimize the risks identified for medicinal products can be:
  - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
  - Important advice on the medicine's packaging;
  - The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
  - The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of YUVANCI, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of YUVANCI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of YUVANCI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	Hepatotoxicity Teratogenicity
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Macitentan, like other medicines of the same class, may affect the liver. The mechanism of this adverse impact is unclear. Interruption or stopping treatment may be necessary. There are no data to support a risk for liver toxicity associated with tadalafil.
Risk factors and risk groups	Unknown in patients with severe hepatic impairment and alanine transaminase (ALT)/ aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN) as they were excluded from Study AC-077A301 (A DUE). Patients with ALT/AST >3×ULN at baseline or with moderate or severe liver impairment are excluded from clinical trials with macitentan.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use).

Important Identified Risk: Hepatotoxicity	
	SmPC Section 4.8 (Undesirable effects). Package Leaflet Section 2 (What you need to know before you take Yuvanci). Package Leaflet Section 4 (Possible side effects). Warning that M/T FDC is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or elevated baseline values of aminotransferases (AST and/or ALT >3×ULN) is given in SmPC Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), and 4.4 (Special warnings and precautions for use). Recommendation that liver enzyme tests be obtained prior to initiation of M/T FDC and repeated monthly during treatment is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation that patients should be monitored for signs of hepatic injury is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation to discontinue M/T FDC if sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical symptoms of liver injury is given in SmPC Section 4.4 (Special warnings and precautions for use). This section also notes that reinitiation of M/T FDC may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury; the advice of a hepatologist is recommended. Warning to patients not to take M/T FDC and to speak to their doctor if they have liver disease or if they have very high levels of liver enzymes in their blood is provided in Package Leaflet Section 2 (What you need to know before you take Yuvanci). Patients are informed that their doctor will carry out laboratory tests to test whether their liver is working properly prior to initiation and during treatment, as needed, with M/T FDC in Package Leaflet Section 2 (What you need to know before you take Yuvanci). Recommendation for patients to speak to their doctor immediately if they notice signs of liver impairment is given in Package Leaflet Section 2 (What you need to know before you take Yuvanci). This section also contains a recommendation for patients to speak to their doctor if they have a severe liver problem before taking M/T FDC. Legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.

Important Identified Risk: Teratogenicity	
Evidence for linking the risk to the medicine	According to results from animal studies, macitentan and medicines of the same class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed.
Risk factors and risk groups	All women of childbearing potential on M/T FDC therapy who are not using a reliable method of contraception.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction). SmPC Section 4.6 (Fertility, pregnancy and lactation). SmPC Section 5.3 (Preclinical safety data). Package Leaflet Section 2 (What you need to know before you take Yuvanci). Warning that use of M/T FDC is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception due to teratogenicity identified in animal studies with macitentan is given in SmPC Section 4.6 (Fertility, pregnancy and lactation). Appropriate text is also given in SmPC Section 4.3 (Contraindications). Recommendation that M/T FDC treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation that women should not become pregnant for 1 month after discontinuation of M/T FDC is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation for use of monthly pregnancy tests during treatment with M/T FDC to allow for early detection of pregnancy is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendations for patients to use a reliable form of birth control (contraception) whilst taking M/T FDC and to not take M/T FDC if they are pregnant, are planning to become pregnant, or could be pregnant because they are not using reliable birth control are given in Package Leaflet Section 2 (What you need to know before you take Yuvanci). Warning that treatment with M/T FDC must not be taken during pregnancy is provided in Package Leaflet Section 2 (What you need to know before you take Yuvanci). This section contains recommendations for patients to consult their doctor immediately if

Important Identified Risk: Teratogenicity	
	they become pregnant or think they may be pregnant while taking M/T FDC or shortly after stopping M/T FDC (up to 1 month). Recommendations for patients to have a pregnancy test before initiation of M/T FDC and every month during treatment are given in Package Leaflet Section 2 (What you need to know before you take Yuvanci). Legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of YUVANCI.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for YUVANCI.

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

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Follow-up Forms

Macitentan-Tadalafil FDC Pregnancy and Outcome Follow-Up Questionnaire

INSTRUCTIONS:

If you are receiving this form and the mother is currently pregnant, please complete Part I. This form will be sent again post-delivery date to obtain pregnancy outcome (Part II). If further additional space is needed, attach a blank continuation page, and enter the information on the continuation page. If a continuation page is needed ensure the local reference number is entered at the top of the continuation page.

If you are receiving this form and the mother has delivered the baby or is no longer pregnant (e.g., spontaneous abortion, elective abortion, etc.), please complete Part II. Please also provide Part I details if not previously completed.

(COMPANY USE ONLY - complete prior to sending to health care professional):	
Operating Company:	J&J Product:
Local Report Number:	Date Received by J&J: (dd/mmm/yyyy)
Originating Country:	MFR # (if available):
Exposure: ☐ Maternal ☐ Paternal	
Protocol number: Double Blind (code not broken): ☐	
Study medication/product:	
Subject number: Site #:	

Part I:

A. MATERNAL INFORMATION			
Initials*: Date of birth*: *This field not to be used for clinical trial reports Age at time of exposure: or Age Group: ☐ <14 years ☐ 14 years – 18 years ☐ 19 years+ Weight: ☐ Kg ☐ Lbs. Height: ☐ Cm ☐ Inches			
Methods of Contraception: Please provide Serial/Model # and expiration date if applicable. 1. 2.			
Were there any relevant maternal risk factors in the home/work environment (such as chemical exposure, x-rays, history of miscarriages, etc.)?	No ☐	Yes ☐	If yes, describe:

B. PRESENT PREGNANCY			
1. Date of mother's last menstrual period: (dd/mmm/yyyy)			
2. Pregnancy confirmed on: (dd/mmm/yyyy) ☐ Beta Hcg ☐ Urine Test			
3. Was the pregnancy test negative at the time of starting Macitentan-Tadalafil? ☐ No ☐ Yes			
4. Date of mother's first prenatal exam: (dd/mmm/yyyy)			
5. Expected date of delivery: (dd/mmm/yyyy)			
6. Is the mother experiencing any medical disorder/problems during this pregnancy?	No ☐	Yes ☐	If yes, describe:
7. Is the mother continuing with Macitentan-Tadalafil? ☐ No ☐ Yes ☐ N/A ☐ Unknown Was the product taken correctly at the time of gestation? ☐ No ☐ Yes If **No**, explain:			

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MFR # [MFR #]

B. PRESENT PREGNANCY

8. Tick the explanation(s) for why the patient became pregnant during the use of Macitentan-Tadalafil:
   - ☐ Patient wished to become pregnant
   - ☐ Failure of contraceptive method(s)
   - ☐ Patient unwilling to use adequate contraceptive methods
   - ☐ Risk of pregnancy may not have been fully understood
   - ☐ Unknown
   - ☐ Other (Specify):

9. List all medications mother used since date of last menstrual period (include J&J products and non-J&J products, prescription, over-the-counter, vitamins, and herbal preparations - list below).

Medication (preferably generic name)	Route	Formulation	Dosing regimen			Start date (dd/mmm/yyyy)	End Date or Ongoing (dd/mmm/yyyy)	Exposure time in gestational weeks	Indication
			Amount	Unit	Freq.				
Macitentan Tadalafil:									
Lot #: **Exp. Date:** (dd/mmm/yyyy)									
Other Medications:									

10. Was an ultrasound performed? ☐ No ☐ Yes — If yes, provide date and results of each ultrasound: (dd/mmm/yyyy)

11. Were any other investigations/diagnostics performed, such as amniocentesis, blood test, urine test, etc.? ☐ No ☐ Yes — If yes, provide date test performed and results of each test. 4 (dd/mmm/yyyy and result)

12. What is the clinical condition of the foetus(es)? — Unknown ☐ Normal ☐ Abnormal ☐ If abnormal, describe:

13. What is the status of the current pregnancy?
   - ☐ Continuing
   - ☐ Spontaneous abortion Date of abortion: (dd/mmm/yyyy)
   - ☐ Elective abortion Date of procedure: (dd/mmm/yyyy)

C. MATERNAL HISTORY

1. Describe pertinent medical/obstetrical history (including but not limited to endocrine disorders, medical disorders or recent infections requiring treatment, infertility, or use of fertility methods):

2. **Substance History**	**No**	**Yes**	**Select all that apply:**
Alcohol	☐	☐	Drinks per day:
Tobacco	☐	☐	Cigarettes per day:
Recreational drugs	☐	☐	Type of drug(s) and frequency:

3. Is there any **family history** of congenital anomalies, significant obstetrical outcomes, or hereditary disorders?	No ☐	Yes ☐	If yes, describe:

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MFR # [MFR #]

D. PREVIOUS PREGNANCIES			
Has mother been pregnant before? No ☐ Yes ☐	Gravida (include present pregnancy):	Para:	Abortions: Induced: Spontaneous: Gestational age: weeks days
	# Of normal outcomes:	# Of abnormal outcomes:	# Of unknown outcomes:
Describe any abnormal outcomes (include spontaneous abortion, ectopic, congenital anomalies, hereditary disorders, stillbirths, or intrauterine death, etc.):			
In case of a previous abnormal pregnancy outcome, list all known medications used during the pregnancy:			

E. PATERNAL HISTORY			
Substance History	**No**	**Yes**	**Select all that apply:**
Alcohol	☐	☐	Drinks per day:
Tobacco	☐	☐	Cigarettes per day:
Recreational drugs	☐	☐	Type of drug(s) and frequency:
Was Macitentan-Tadalafil used by father?	No ☐	Yes ☐	

Health Care Professional Information:

Name:
Address:
Phone number:
Fax number:

Signature
Date: (dd/mmm/yyyy)

Person Completing Report:

Name:
Address:
Phone number:
Fax number:

Signature
Date: (dd/mmm/yyyy)

MFR # [MFR #]

Part II:

A. COURSE AND OUTCOME OF PREGNANCY			
1. Did the mother experience any medical problems during the pregnancy?	**No** ☐	**Yes** ☐	If yes, describe:
Complete the below question if there were changes since completion of corresponding section in Part I. ☐ **No Changes**			

2. List all medications the mother has used since last menses, until day of delivery. (Include J&J product and non-J&J products, prescription, over-the counter, vitamins, and herbal preparations, but exclude medication used during labor and delivery.)

Medication (preferably generic name)	Route	Formulation	Dosing regimen			Start date (dd/mmm/yyyy)	End date or ongoing (dd/mmm/yyyy)	Exposure time in gestational weeks	Indication
			Amt	Unit	Freq				
Macitentan-Tadalafil:									
Lot #: **Exp. Date:** (dd/mmm/yyyy)									
Other Medications:									

3. Did the mother receive any **medication during labor and delivery**? (Include anesthesia, analgesia, labor induction meds.)

Medication (preferably generic name)	Route	Formulation	Dosing regimen			Start date (dd/mmm/yyyy)	End date or ongoing (dd/mmm/yyyy)	Indication
			Amt	Unit	Freq			

4. Specify the outcome of pregnancy and complete the rest of the form as applicable:		
a) Interrupted pregnancy No ☐ Yes ☒	☐ Spontaneous Abortion	(dd/mmm/yyyy)
	☐ Elective Abortion	(dd/mmm/yyyy)
	☐ Intrauterine Death (≥20 Gestational Weeks)	Interruption date: (dd/mmm/yyyy) Gestational age: Weeks Days
Specify suspected cause for intrauterine death or spontaneous abortion (autopsy report if done)		
Describe the developmental status of the fetus (include anomalies)		
b) Uninterrupted pregnancy:	Delivery date: (dd/mmm/yyyy)	
	Gestational age: Weeks Days	
What was the method of delivery?	☐ Spontaneous ☐ Forceps ☐ Vacuum Extraction ☐ Caesarean Section ☐ Other, specify :	

MFR # [MFR #]

B. CHARACTERISTICS OF THE BABY				
1. General appearance: ☐ Mature			☐ Premature	☐ Postmature
2. Sex: ☐ Male ☐ Female	Weight: lbs./kg oz/g		Length: in/cm	Head circumference: in/cm
Apgar score: 1min:	5min:	10min:		
3. Clinical condition of the baby:				
☐ Normal newborn				
☐ Congenital anomaly*				
☐ Neonatal problem*				
☐ Neonatal death* ☐ Stillbirth*	Date of death: (dd/mmm/yyyy)			
*Describe the details and the probable cause for the abnormal outcome:				
	No	Yes		
4. Was the baby's hospitalization prolonged?	☐	☐	If yes, describe:	
5. Did the baby receive any medical therapy different from normal newborn care?	☐	☐	If yes, describe:	
6. Is the baby being breastfed?	☐	☐		
7. Was any relationship suspected between the abnormal pregnancy outcome and the use of the Macitentan-Tadalafil?			☐ Not related	☐ Related
8. Was any relationship suspected between the abnormal pregnancy outcome and the use of concomitant medications? ☐ No ☐ Yes (if yes, describe)			Describe:	

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Annex 6: Details of Proposed Additional Risk Minimization Activities

Proposed Key Messages of the Additional Risk Minimization Measures

1. Patient Card:

The Patient Card includes the following key messages:

- That YUVANCI is teratogenic in animals;
- That pregnant women must not take YUVANCI;
- That women of childbearing potential must use reliable contraception;
- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because YUVANCI has hepatotoxic potential.