EU Risk Management Plan

For

Macitentan AccordPharma 10 mg film-coated tablets (Macitentan)

RMP version to be assessed as part of this application:

RMP Version number	1.2
Data lock point for this RMP	28-Jan-2025
Date of final sign off	04-Feb-2025

Rationale for submitting an RMP: Risk Management Plan (RMP) has been updated as per product information has been updated to in line with the revised SmPC.

Summary of significant changes in this RMP: Significant changes have been done in the following section of this RMP: Part I, Part VI and Part VII (Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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QPPV Signature: 

TABLE OF CONTENT

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LIST OF TABLES

[redacted]

Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Macitentan
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension **ATC code:** C02KX04
Marketing Authorisation Holder	Accord Healthcare S.L.U, Spain
Medicinal products to which this RMP refers	01
Invented name(s) in the European Economic Area (EEA)	Macitentan AccordPharma 10 mg film-coated tablets
Marketing authorisation procedure	EMEA/H/C/6523
Brief description of the product	Chemical class: Macitentan is a member of the class of sulfamides in which the two amino groups of sulfonamide are substituted by 5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl) oxy]ethoxy} pyrimidin-4-yl and propyl groups.
	Summary of mode of action: Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

[redacted]

	Macitentan is an orally active potent endothelin receptor antagonist, active on both ETA and ETB receptors and approximately 100-fold more selective for ETA as compared to ETB in vitro. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial= smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
	Important information about its composition: Each film-coated tablet contains 10 mg macitentan. *Excipients with known effect:* Each film-coated tablet contains approximately 38 mg of lactose monohydrate and approximately 0.06 mg of lecithin [Soya].
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL
Indication(s) in the EEA	***Current*** Adults Macitentan AccordPharma, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Paediatric population Macitentan AccordPharma, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ⩾ 40 kg with WHO Functional Class (FC) II to III.

[redacted]

Dosage in the EEA	***Current*** Posology: The recommended dose is 10 mg once daily. Macitentan AccordPharma should be taken every day at about the same time. If the patient misses a dose of Macitentan AccordPharma, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should be told not to take two doses at the same time if a dose has been missed. The 10 mg film-coated tablets are only recommended in paediatric patients weighing at least 40 kg. Method of administration Macitentan should be administered orally, to be swallowed whole, with water.
Pharmaceutical forms and strengths	***Current*** Film-coated tablet 10 mg
Is the product subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable

Part II: Module SIII - Clinical trial exposure

Not applicable

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been updated as per CHMP day 120 list of questions for Macitentan Accord (EMEA/H/C/6523) dated 19-Sep-2024.

Hence this section remains “Not applicable”.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

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

SVII.3.1. Presentation of important identified risks and important potential risks

Not Applicable

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Hepatotoxicity • Teratogenicity
Important potential risks	• None
Missing information	• None

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concern listed in module SVIII.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for following risks concerning use of macitentan:
    - Teratogenicity

Purpose: Risk wise description is provided as follows:

- Each pregnancy to be followed up to final outcome. Pregnancy information (including maternal and baby information) is collected using the Macitentan Pregnancy and Outcome Follow-Up Questionnaire.

Targeted follow-up questionnaires and data collection forms are appended in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

\Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important identified risks	
Hepatotoxicity	Routine risk communication: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • 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 x ULN, or by clinical symptoms of liver injury (e.g. jaundice), macitentan treatment should be discontinued, is included in SmPC section 4.4. • Reinitiation of macitentan 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, is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • The prescription only status of the product
Teratogenicity	Routine risk communication: • SmPC sections 4.3, 4.4 and 4.6

[redacted]

	• PL section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • Macitentan 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 practised, is included in SmPC sections 4.3 and 4.6. • Women should not become pregnant for 1 month after discontinuation of macitentan. Monthly pregnancy tests during treatment with macitentan are recommended to allow the early detection of pregnancy, is included in SmPC section 4.4. <u>Other routine risk minimisation measures beyond the Product Information:</u> • The prescription only status of the product.

[redacted]

V.2. Additional Risk Minimisation Measures

In line with reference medicinal product, Additional Risk Minimisation Measures (aRMMs) have been proposed for following risks:

- Teratogenicity
- Hepatotoxicity

Proposed additional risk minimisation measures are listed below and key messages are summarised in Annex 6.

Additional risk minimisation

Patient Alert Card

Objectives:

The overall goal of the 'Patient Alert Card' is:

- To educate patients on important safety information related to teratogenicity and hepatotoxicity that they need to be aware of before and during treatment with macitentan.
- 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 ADR.

Rationale for the additional risk minimisation activity:

These efforts reinforce patient knowledge regarding the safe minimisation activity: use of macitentan, thereby mitigating the risks associated with macitentan treatment.

Target audience and planned distribution path:

All the patients who may consume or are prescribed macitentan.

Patients should be provided with the package leaflet and the 'Patient Alert Card' which are included in the pack.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities involving analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of this measure will be analysed by MAH as per the requirements for

[redacted]

submission of periodic safety update reports (PSUR) for this medicinal product as per local country specific requirement or as set out in the list of European Union Reference Dates (EURD list) provided as per Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency's web-portal and also will be evaluated in details in periodic signal management activity.

[redacted]

V.3 Summary of risk minimisation measures

Table 4: Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Routine Risk Minimisation Activities	Pharmacovigilance activities
Important identified risks		
Hepatotoxicity	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • 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 x ULN, or by clinical symptoms of liver injury (e.g. jaundice), macitentan treatment should be discontinued, is included in SmPC section 4.4. • Reinitiation of macitentan 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, is included in SmPC section 4.4. • The prescription only status of the product	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

[redacted]

	Additional risk minimisation measures: Risk minimisation tools (Patient card)	
Teratogenicity	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.6 • PL section 2 • Macitentan 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 practised, is included in SmPC sections 4.3 and 4.6. • Women should not become pregnant for 1 month after discontinuation of macitentan. Monthly pregnancy tests during treatment with macitentan are recommended to allow the early detection of pregnancy, is included in SmPC section 4.4. • The prescription only status of the product Additional risk minimisation measures: • Risk minimisation tools (Patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Macitentan Pregnancy and Outcome Follow-Up Questionnaire. Additional pharmacovigilance activities: None.

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Macitentan AccordPharma 10 mg film-coated tablets (Macitentan)

This is a summary of the risk management plan (RMP) for Macitentan AccordPharma 10 mg film-coated tablets. The RMP details important risks of Macitentan AccordPharma 10 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Macitentan AccordPharma 10 mg film-coated tablets' risks and uncertainties (missing information).

Macitentan AccordPharma 10 mg film-coated tablets' summary of product characteristics (SmPC) and package leaflets give essential information to healthcare professionals and patients on how Macitentan AccordPharma 10 mg film-coated tablets should be used.

This summary of the RMP for Macitentan AccordPharma 10 mg film-coated tablets 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 Macitentan AccordPharma 10 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Adults

Macitentan AccordPharma 10 mg film-coated tablets, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

Paediatric population

Macitentan AccordPharma, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III.

It contains macitentan as the active substance and it is administered by oral route.

Further information about the evaluation of Macitentan AccordPharma 10 film-coated tablets benefits can be found in Macitentan AccordPharma 10 mg film-coated tablets EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

[redacted]

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Macitentan AccordPharma 10 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Macitentan AccordPharma 10 mg film-coated tablets' risks, are outlined below.

Measures to minimise 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 authorised 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Macitentan AccordPharma 10 mg film-coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Macitentan AccordPharma 10 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise 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 Macitentan AccordPharma 10 mg film-coated tablets. 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 (e.g. on the long-term use of the medicine).

[redacted]

Important identified risks	• Hepatotoxicity • Teratogenicity
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • 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 x ULN, or by clinical symptoms of liver injury (e.g. jaundice), macitentan treatment should be discontinued, is included in SmPC section 4.4. • Reinitiation of macitentan 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, is included in SmPC section 4.4. • The prescription only status of the product Additional risk minimisation measures: Risk minimisation tools (patient card)
Important Identified Risk: Teratogenicity	

[redacted]

Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.6 • PL section 2 • Macitentan 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 practised, is included in SmPC sections 4.3 and 4.6. • Women should not become pregnant for 1 month after discontinuation of macitentan. Monthly pregnancy tests during treatment with macitentan are recommended to allow the early detection of pregnancy, is included in SmPC section 4.4. • The prescription only status of the product Additional risk minimisation measures: Risk minimisation tools (patient card)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Macitentan AccordPharma 10 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Macitentan AccordPharma 10 mg film-coated tablets.

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed following targeted follow-up questionnaires

- Pregnancy and Outcome Follow-Up Questionnaire

Macitentan 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.

Part I

A. MATERNAL INFORMATION			
Initials: Date of birth: (dd/mmm/yyyy) Age at time of exposure: Or Age Group: ☐<14 Years ☐ 14-18 Years 19Years+ ☐ 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? ☐ 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 ? No ☐ Yes ☐ N/A ☐ Unknown
   Was the product taken correctly at the time of gestation? ☐ No ☐ Yes
   If No, explain:

8. Tick the explanation(s) for why the patient became pregnant during the use of Macitentan:
   ☐ Patient wished to become pregnant
   ☐ Patient unwilling to use adequate contraceptive methods
   ☐ Failure of contraceptive method(s)
   ☐ 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 all the products, prescription, over-the-counter, vitamins, and herbal preparations list below).

Medicaton (preferaby generic name)	Route	Formulation	Dosing regimen			Start date (dd/mmm/yyyy)	End Date or Ongoing (dd/mmm/yyyy)	Exposure time in gestation al weeks	Indication
			Amount	Unit	Frequency				
Macitentan:									
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/mm/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. (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:

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, ectopics, 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 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)

Part II

A. COURSE AND OUTCOME OF PREGNANCY			
1. Did the Mother experience any medical problems during the pregnancy?	Yes ☐	No ☐	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 all the 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
			Amount	Unit	Frequency				
Macitentan:									
Lot #: Exp. Date: (dd/mmm/yyyy)									
Other Medication:									

3. Did the mother receive any medication during labour and delivery? (Include anaesthesia, analgesia, labour induction meds)

Medication (preferably generic name)	Route	Formulation	Dosing regime			Start date (dd/mmm/yyyy)	End Date or Ongoing (dd/mmm/yyyy)	Indication
			Amount	Unit	Frequency			

4. Specify the outcome of pregnancy and complete the rest of the form as applicable:		
a) Interrupted pregnancy ☐ Yes ☐ No	☐ Spontaneous Abortion	(dd/mm/yyyy)

	☐ Elective Aborton	(dd/mm/yyyy)
	☐ Intrauterine Death (≥20 Gestational Weeks)	Interruption date: (dd/mm/yyyy) Gestational age: Weeks Days
Specify suspected cause for intrauterine death or spontaneous abortion (autopsy		
Describe the developmental status of the fetus (include anomalies)		
b) Uninterrupted pregnancy:	Delivery date (dd/mm/yyyy)	
	Gestational age: Weeks Days	
What was the method of delivery?	☐ Spontaneous ☐ Forceps ☐ Vacuum Extraction ☐ Caesarean Section	

B. CHARACTERISTICS OF THE BABY			
1. General appearance:	☐ Mature	☐ Premature	☐ Postmature
2. Sex: ☐ Male ☐ Female Head circumference:	Weight: cm	lbs/kg oz/g	Length: in/cm
Apgar score: 1min: 5min: 10min:			
3. Clinical condition of the babv:			
☐ Normal Newborn			
☐ Conginental Anomaly*			
☐ Neonatal Problem*			
☐ Neonatal Death* ☐	Date of death (dd/mmm/yyyy)		
*Describe the details and the probable cause for the abnormal outcome:			
4. Was the baby's hospitalisation prolonged?	No ☐	Yes ☐	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?	☐ Not related	☐ Related	
8. Was any relationship suspected between the abnormal pregnancy outcome and the use of concomitant medication? ☐ No ☐ Yes (if yes, describe)	Describe:		

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Prior to the launch of Macitentan AccordPharma 10 mg film-coated tablets in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material with the National Competent Authority.

The MAH shall ensure that in each Member State where Macitentan AccordPharma 10 mg film-coated tablets is marketed, all patients who are expected to use Macitentan AccordPharma 10 mg film-coated tablets are provided with the following educational material:

- Patient Card

The Patient Alert Card to be held by the patient. The overall goal of the Patient Alert Card is to educate patients on important safety information that they need to be aware of before and during treatment with macitentan.

1. **Patient card:**

The patient card includes the following key elements:

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