EU Risk Management Plan

for

Dasatinib Accord Healthcare 20 mg film-coated tablets

Dasatinib Accord Healthcare 50 mg film-coated tablets

Dasatinib Accord Healthcare 70 mg film-coated tablets

Dasatinib Accord Healthcare 80 mg film-coated tablets

Dasatinib Accord Healthcare 100 mg film-coated tablets

Dasatinib Accord Healthcare 140 mg film-coated tablets

(Dasatinib)

RMP version to be assessed as part of this application:

RMP Version number	1.1
Data lock point for this RMP	30-Oct-2023
Date of final sign off	11-Dec-2023

Rationale for submitting an updated RMP: RMP has been updated as per PRAC Rapporteur Risk Management Plan (RMP) Assessment Report of Dasatinib Accord Healthcare, (EMEA/H/C/0006251), dated 17-Aug-2023 and Sprycel® (Dasatinib) RMP version 17.0 published dated 30-Oct-2023.

Summary of significant changes in this RMP: Significant changes have been updated in following sections of RMP: Part I, Part II (Module SVII and Module SVIII), Part V, Part VI II.A, Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

QPPV name: Agata Gesiewicz

QPPV signature: [redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES **5**
Part I: Product(s) Overview **6**
Each film-coated tablet contains 174.6 mg of lactose **8**
Part II: Safety specification **11**
Module SI – Epidemiology of the indication(s) and target population(s) 11
Module SII – Non-clinical part of the safety specification 11
Module SIII – Clinical trial exposure 11
Module SIV – Populations not studied in clinical trials 11
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme 11
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 11
SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes 11
Module SV – Post-authorisation experience 11
SV.1 Post-authorisation exposure 11
Module SVI – Additional EU requirements for the safety specification 11
Module SVII – Identified and potential risks 12
SVII.1 Identification of safety concerns in the initial RMP submission 12
SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP 12
SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP 12
SVII.2 New safety concerns and reclassification with a submission of an updated RMP 12
SVII.3 Details of important identified risks, important potential risks, and missing information 12
SVII.3.1 Presentation of important identified risks and important potential risks 12
SVII.3.2 Presentation of the missing information 12
Module SVIII – Summary of the safety concerns 13
Part III: Pharmacovigilance Plan (including post-authorisation safety studies) **14**
III.1 Routine pharmacovigilance activities 14
III.2 Additional pharmacovigilance activities 14
III.3 Summary Table of additional Pharmacovigilance activities 14
Part IV: Plans for post-authorisation efficacy studies **15**
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) **16**
V.1 Routine Risk Minimisation Measures 16
V.2. Additional Risk Minimisation Measures 16
V.3 Summary of risk minimisation measures 16
Part VI: Summary of the risk management plan **17**
I. The medicine and what it is used for 17

II. Risks associated with the medicine and activities to minimise or further characterise the risks 18
II.A List of important risks and missing information 18
II.B Summary of important risks 20
II.C Post-authorisation development plan 20
II.C.1 Studies which are conditions of the marketing authorisation 20
II.C.2 Other studies in post-authorisation development plan 20
Part VII: Annexes 21
Annex 1 – EudraVigilance Interface 22
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 22
Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 22
Annex 4 – Specific adverse drug reaction follow-up forms 23
Annex 5 – Protocols for proposed and on-going studies in RMP part IV 40
Annex 6 – Details of proposed additional risk minimisation activities 40
Annex 7 – Other supporting data (including referenced material) 40
Annex 8 – Summary of changes to the risk management plan over time 41

LIST OF TABLES

Table 1: Product Overview..... 6
Table 2: Summary of safety concerns 13
Table 3: Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection ... 14

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Dasatinib
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group**: Antineoplastic agents, Protein kinase inhibitors **ATC Code** :(L01EA02)
Marketing Authorisation Applicant	Accord Healthcare S.L.U. Spain
Medicinal products to which this RMP refers	06
Invented name(s) in the European Economic Area (EEA)	Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/0006251)
Brief description of the product	Chemical Class*:* Pyrimidine and Thiazole derived Antineoplastic agent and Protein kinase inhibitor.
	Summary of mode of action: *In vitro*, dasatinib is active in leukaemic cell lines representing variants of imatinib-sensitive and resistant disease. These non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations.

	In vivo, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient-derived CML cell lines grown at various sites, including the central nervous system.
	Important information about its composition: Dasatinib Accord Healthcare 20 mg film-coated tablets Each film-coated tablet contains 20 mg of dasatinib (as monohydrate) *Excipient with known effect* Each film-coated tablet contains 25 mg of lactose. Dasatinib Accord Healthcare 50 mg film-coated tablets Each film-coated tablet contains 50 mg of dasatinib (as monohydrate) *Excipient with known effect* Each film-coated tablet contains 62.4 mg of lactose. Dasatinib Accord Healthcare 70 mg film-coated tablets Each film-coated tablet contains 70 mg of dasatinib (as monohydrate). *Excipient with known effect* Each film-coated tablet contains 87.3 mg of lactose. Dasatinib Accord Healthcare 80 mg film-coated tablets Each film-coated tablet contains 80 mg of dasatinib (as monohydrate). *Excipient with known effect* Each film-coated tablet contains 99.8 mg of lactose.

	Dasatinib Accord Healthcare 100 mg film-coated tablets Each film-coated tablet contains 100 mg of dasatinib (as monohydrate). *Excipient with known effect* Each film-coated tablet contains 124.7 mg of lactose. Dasatinib Accord Healthcare 140 mg film-coated tablets Each film-coated tablet contains 140 mg of dasatinib (as monohydrate). *Excipient with known effect* Each film-coated tablet contains 174.6 mg of lactose.
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC.
Indication(s) in the EEA	***Current*** Dasatinib Accord Healthcare is indicated for the treatment of adult patients with: • newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. • chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib. • Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy. Dasatinib Accord Healthcare is indicated for the treatment of paediatric patients with: • newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.

	• newly diagnosed Ph+ ALL in combination with chemotherapy.
Dosage in the EEA	***Current*** Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukemia. **Posology:** *Adult patients* The recommended starting dose for chronic phase CML is 100 mg dasatinib once daily. The recommended starting dose for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 140 mg once daily. *Paediatric population* (Ph+ CML-CP and Ph+ ALL) Dosing for children and adolescents is on the basis of body weight, see the below table. Dasatinib is administered orally once daily in the form of either Dasatinib Accord Healthcare film-coated tablets or Dasatinib powder for oral suspension. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with Dasatinib Accord Healthcare film-coated tablets treatment in children under 1 year of age. Dasatinib Accord Healthcare film-coated tablets and Dasatinib powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from Dasatinib powder for oral suspension to Dasatinib Accord Healthcare film-coated tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so,

<table>
<tr><td></td><td>provided that the correct dosing recommendations for the dosage form are followed.

Table 1: Dosage of Dasatinib film-coated tablets for paediatric patients with Ph+ CML-CP or Ph+ ALL
<table>
<tr><th>Body weight (kg)</th><th>Daily dose (mg)</th></tr>
<tr><td>10 to less than 20 kg</td><td>40 mg</td></tr>
<tr><td>20 to less than 30 kg</td><td>60 mg</td></tr>
<tr><td>30 to less than 45 kg</td><td>70 mg</td></tr>
<tr><td>at least 45 kg</td><td>100 mg</td></tr>
</table>
<u>Method of administration</u>

Dasatinib Accord Healthcare must be administered orally.

The film-coated tablets must not be crushed, cut or chewed in order to maintain dosing consistency and minimise the risk of dermal exposure; they must be swallowed whole. Film-coated tablets should not be dispersed as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet. Dasatinib Accord Healthcare can be taken with or without a meal and should be taken consistently either in the morning or in the evening. Dasatinib Accord Healthcare should not be taken with grapefruit or grapefruit juice.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current

Film-coated tablet.

20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg</td></tr>
<tr><td>Is the product subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

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

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

Module SVII – Identified and potential risks

There is a published Risk Management Plan available for the reference originator product Sprycel® (Dasatinib) RMP version 17.0 published by EMA on 30-Oct-2023. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII, which are in-line with RMP summary of originator product (Sprycel ®).

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

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Myelosuppression • Fluid Retention • Bleeding Related Events • QT Prolongation • Pulmonary Arterial Hypertension (PAH) • Pregnancy Related Malformative or Foeto/ Neonatal Toxicity • Nephrotic Syndrome • Thrombotic Microangiopathy
Important potential risks	• Severe Hepatotoxicities • Direct Cardiotoxic Effects (e.g., Cardiomyopathy) • Growth and development disorders and bone mineral metabolism disorders in the paediatric population • Toxic Skin Reactions • CYP3A4 drug interactions • HBV reactivation
Missing information	• Carcinogenicity • Paediatric data: Children < 1 year of age • Reproductive and lactation data

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 this medicinal product.

There is no PSUR requirement as per EURD for Generic Application [Article 10(1)], hence Accord shall monitor both "direct cardiotoxic effects" and "growth and development disorders and bone mineral metabolism disorders in the paediatric population" through routine pharmacovigilance activity (ICSR reporting and Signal Management activity).

Other routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are summarised in Table 3.

Table 3: Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Specific adverse reaction follow-up questionnaires	
Specific adverse reaction follow-up questionnaires for PAH	Use of Dasatinib Pulmonary Arterial Hypertension (PAH) Questionnaires (Annex 4) to collect additional clinical and diagnostic information on reported PAH during dasatinib exposure in order to characterise the event and outcomes.
Specific adverse reaction follow-up questionnaires for HBV reactivation	Adverse event report questionnaire will systematically collect targeted clinical and treatment information for individual case safety reports (Annex 4).

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

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

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

None proposed.

V.3. Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets (dasatinib)

This is a summary of the risk management plan (RMP) for Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets. The RMP details important risks of Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets' risks and uncertainties (missing information).

Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets should be used.

This summary of the RMP for Accord Healthcare 20/50/70/80/100/140 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 Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Dasatinib Accord Healthcare is indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Dasatinib Accord Healthcare is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

It contains dasatinib as the active substance and it is given orally.

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

Important risks of Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets together with measures to minimise such risks and the proposed studies for learning more about Dasatinib Accord Healthcare 20/50/70/80/100/140 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 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*.

If important information that may affect the safe use of Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dasatinib Accord Healthcare 20/50/70/80/100/140 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 Dasatinib Accord Healthcare 20/50/70/80/100/140 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).

Important identified risks	• Myelosuppression • Fluid Retention • Bleeding Related Events • QT Prolongation • Pulmonary Arterial Hypertension (PAH) • Pregnancy Related Malformative or Foeto/ Neonatal toxicity • Nephrotic Syndrome • Thrombotic Microangiopathy
Important potential risks	• Severe Hepatotoxicities • Direct Cardiotoxic Effects (e.g., Cardiomyopathy) • Growth and development disorders and bone mineral metabolism disorders in the paediatric population • Toxic Skin Reactions • CYP3A4 Drug Interactions • HBV Reactivation
Missing information	• Carcinogenicity • Paediatric data: Children < 1 year of age • Reproductive and lactation data

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

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 Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets.

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

There are no studies required for Dasatinib Accord Healthcare 20/50/70/80/100/140 mg film-coated tablets.

Annex 4 – Specific adverse drug reaction follow-up forms

In line with reference product, MAH has developed specific adverse reaction follow-up questionnaires as following:

- Adverse Event Report Questionnaire: Hepatitis B Reactivation Questionnaire
- Dasatinib Pulmonary Hypertension (PH) Follow-Up Form

DASATINIB PULMONARY HYPERTENSION FOLLOW-UP FORM

EVENT IDENTIFICATION

PULMONARY HYPERTENSION

☐ NSAE (Non-serious Adverse Event)
☐ SAE (Serious Adverse Event)

Adverse Event Clinical Diagnosis (Verbatim Term)

Date of Onset
DD-MMM-YYYY

PRESENTING SIGNS AND SYMPTOMS OF PH

Complete for all patients. Do not mark this page as blank

Signs and Symptoms **Symptoms?**

DYSPNEA

☐ NO
☐ YES
☐ UNKNOWN

Specify

Signs and Symptoms **Symptoms?**

PERIPHERAL EDEMA

☐ NO
☐ YES
☐ UNKNOWN

Specify

Signs and Symptoms **Symptoms?**

ABDOMINAL PAIN

☐ NO
☐ YES
☐ UNKNOWN

Specify

Signs and Symptoms	**Symptoms?**
FATIGUE	☐ NO ☐ YES ☐ UNKNOWN

Specify

Signs and Symptoms	**Symptoms?**
SYNCOPE	☐ NO ☐ YES ☐ UNKNOWN

Specify

Signs and Symptoms	**Symptoms?**
CHEST PAIN	☐ NO ☐ YES ☐ UNKNOWN

Specify

Signs and Symptoms	**Symptoms?**
WEAKNESS	☐ NO ☐ YES ☐ UNKNOWN

Specify

Signs and Symptoms	**Symptoms?**
OTHER	☐ NO ☐ YES ☐ UNKNOWN

If Yes, **Specify**

[redacted]

2D ECHOCARDIOGRAM

Was 2D echocardiogram performed? ☐ NO ☐ YES *if yes, complete below*

Date 2D echocardiogram was performed DD-MMM-YYY

Left ventricular ejection fraction **%**

Interpretation of 2D echocardiogram valvular assessment ☐ NORMAL ☐ ABNORMAL

Mean PAP nn mmHg

Mean Systolic PAP nn mmHg

Mean Diastolic PAP nn mmHg

Tricuspid Regurgitation Velocity nn m/Sec

[redacted]

PROCEDURES

Complete for all patients. Do not mark this page as blank

Procedure CHEST X-RAY

Location

Was Procedure Performed?

☐ NO
☐ YES

Date (DD-MMM-YYYY)

Interpretation

☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

Procedure POLYSOMNOGRAM

Location

Was Procedure Performed?

☐ NO
☐ YES

Date (DD-MMM-YYYY)

Interpretation

☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

Procedure OVERNIGHT OXIMETRY

Location

Was Procedure Performed?

☐ NO
☐ YES

Date (DD-MMM-YYYY)

Interpretation

☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

[redacted]

Procedure
PULMONARY ANGIOGRAM

Location

Was Procedure Performed?

☐ NO
☐ YES

Date (DD-MMM-YYYY)

Interpretation
☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

Procedure
CHEST CT SCAN

Location

Was Procedure Performed?

☐ NO
☐ YES

Date (DD-MMM-YYYY)

Interpretation
☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

[redacted]

6 MINUTE WALK TEST

Was test performed? ☐ NO ☐ YES *if yes, complete below*

Date of exam DD-MMM-YYYY

Distance walked ☐ FEET ☐ METERS

Dyspnea on exertion *(Borg scale 0-10 point)*

02 SATURATION AT START

%

02 SATURATION LOWEST RECORDED

%

OXYGEN DELIVERY RATE

1/min

[redacted]

PULMONARY FUNCTION TEST

SPIROMETRY

Was spirometry test performed? ☐ NO ☐ YES *if yes, complete below*

Date of exam DD-MMM-YYY

FVC	n.nn	L
FEV1	n.nn	L
TLC	n.nn	L
FRC	n.nn	L

DLCO

Was DLCO test performed? ☐ NO ☐ YES *if yes, complete below*

Date of exam DD-MMM-YYY

DLCO	nn.nn	mL/min/mmHg

[redacted]

RIGHT HEART CATHETERISATION

Do not include additional details such as comments with the responses.
Enter a zero (0) only, if it's a measured test result.

Were any of following protocol specified activities performed?

☐ NO ☐ YES *if yes, complete below*

Date of collection DD-MMM-YYYY

	Result	Unit
MEAN PAP		mmHg
SYSTOLIC PAP		mmHg
DIASTOLIC PAP		mmHg
PULMONARY CAPILLARY WEDGE PRESSURE		mmHg
RIGHT ATRIAL PRESSURE		mmHg
RIGHT VENTRICULAR PRESSURE		mmHg
CARDIAC OUTPUT		L/min
CARDIAC INDEX		L/min
MIXED VENOUS OXYGEN SATURATION (SvO2)		%
PULMONARY VASCULAR RESISTANCE		mmHg/L/min

VASOREACTIVITY

Was vasoreactivity performed? ☐ NO ☐ YES *if yes, complete below*

Date performed DD-MMM-YYYY

Agent

Vasodilation present? ☐ NO ☐ YES

VENTILATION/PERFUSION SCAN

Was ventilation/perfusion scan? ☐ NO ☐ YES *if yes, complete below*

Date of procedure DD-MMM-YYYY

Interpretation ☐ NORMAL ☐ ABNORMAL

Was there a V/Q mismatch? ☐ NO ☐ YES

If yes, describe V/Q mismatch

MEDICAL TREATMENT PROCEDURES FOR PH

Did the subject receive medical treatment procedures for PH?

☐ NO ☐ YES *if yes, complete below*

Procedure *(Specify one per row)*

Ensure these procedures are also recorded on the appropriate CRF pages

REVISED WHO CLASSIFICATION OF PULMONARY HYPERTENSION

Was the revised WHO classification used to assess pulmonary hypertension?

☐ NO ☐ YES *if yes, complete below*

Date of assessment DD-MMM-YYYY

Revised WHO class (PAH))

☐ CLASS 1 (PULMONARY ARTERIAL HYPERTENSION

☐ CLASS 2 (PULMONARY HYPERTENSION WITH LEFT HEART DIESEASE)

☐ CLASS 3 (PULMONARY HYPERTENSION ASSOCIATED WITH LUNG DUSEASE AND/OR HYPOXIA)

☐ CLASS 4 (PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE (CTEPH))

☐ CLASS 5 (MISCELLANEOUS)

RISK FACTORS FOR PH

Does the subject have any of the risk factors for PH listed below?

☐ NO ☐ YES ☐ UNKNOWN *if yes, complete below*

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence (dd-mmm-yyyy)
CONNECTIVE TISSUE DISEASE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
HIV INFECTION	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence

CHRONIC LIVER DISEASE	☐ NO ☐ YES ☐ UNKNOWN	**(dd-mmm-yyyy)**

Specify Risk Factor Details

Risk Factor	**Risk Factor Present?**	**Onset date of Most Recent Occurrence (dd-mmm-yyyy)**
SCHISTOSOMIASIS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	**Risk Factor Present?**	**Onset date of Most Recent Occurrence (dd-mmm-yyyy)**
PULMONARY CAPILLARY HEMANGIOMATOSIS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	**Risk Factor Present?**	**Onset date of Most Recent Occurrence (dd-mmm-yyyy)**
CARDIAC CONDITIONS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	**Risk Factor Present?**	**Onset date of Most Recent Occurrence (dd-mmm-yyyy)**
LUNG DISEASE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

[redacted]

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
HEMATOLOGIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
SYSTEMIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
METABOLIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
CHRONIC RENAL FAILURE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
TUMORAL OBSTRUCTION	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

[redacted]

Risk Factor	Risk Factor Present?	Onset date of Most Recent Occurrence (dd-mmm-yyyy)
SUBSTANCE ABUSE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

SUSPECT MEDICATION FOR PH

Did subject receive suspect medication for PH?
☐ NO ☐ YES *if yes, complete below*

Medication *(List one per row)*
Use generic name whenever possible; use brand name for combination product.

ADVERSE EVENT REPORT QUESTIONNAIRE: HEPATITIS B REACTIVATION

PLEASE PROVIDE THE INFORMATION CHECKED (X) BELOW FOR THE REPORTED ADVERSE EVENT(S):

1. Patient's date of birth or age: Gender:
2. Please provide suspect product(s) those product(s) that are suspected to be associated with one or more adverse events:
3. Daily dose of the suspect product(s): and regimen:
4. Route of administration:
5. Indication(s) for which the suspect product(s) was (were) prescribed:

6. Starting and stop dates of treatment/ treatment duration

7. Lot/Batch number(s) and Expiration date(s)
8. Provide any other suspect medications, not listed above, that may have contributed to the occurrence of the adverse event (s), including indication for which they were prescribed and treatment dates:

9. Please provide details of adverse event(s):
    a. Start date if known:
    b. Time lag if adverse event(s) occurred after cessation of treatment with the suspect product(s):

    c. Signs and symptoms in chronological order:

10. Diagnostic tests (provide test names, dates, results and normal ranges (include units) as well as pre-treatment results if available):

11. Final diagnosis:

12. Did the event require hospitalisation? If yes, specify which event

13. Treatment of adverse event(s):

14. Adverse event(s) stop date and outcome (information on recovery and sequelae, if any):

15. For fatal outcome, please provide cause of death and a comment on its possible relationship to the suspect product(s):

16. Did the adverse event(s) abate after use stopped or dose reduced (if applicable)?

17. Did the adverse event(s) reappear after re-introduction of the suspect product(s) (if applicable)?

18. Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

19. Please list any concomitant medications:
    a. Medication name,
    b. Daily dose/regimen,
    c. Indication;
    d. Start/stop date
    e. Time or duration

20. Are there any other etiological factors: relevant medical and/or drug history (please specify), family history (please specify) and drug/alcohol/tobacco abuse if applicable:

21. Additional questions:
    - Did the patient have past history of HBV or other hepatitis viral infection?
    - Please provide baseline LFT, HBV DNA levels and HBV serology, including HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc.
    - Please provide LFT, HBV DNA and HBV serology data collected during the event.
    - Please provide details regarding the hepatitis B treatment medication, duration and treatment outcome.
    - Did the patient have concurrent use of any immunosuppressant, such as rituximab or ofatumumab?
    - Did the patient ever use any other tyrosine kinase inhibitor such as Imantinib prior to the event?

Health Practitioner Name (Print)_____

Health Practitioner Name (Signature)_____

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable