EU/UK Risk Management Plan

For

Nilotinib Accord 50 mg hard capsules

Nilotinib Accord 150 mg hard capsules

Nilotinib Accord 200 mg hard capsules

Nilotinib 50 mg hard capsules

Nilotinib 150 mg hard capsules

Nilotinib 200 mg hard capsules

(Nilotinib)

RMP version to be assessed as part of this application:

RMP Version number	1.0
Data lock point for this RMP	17-May-2023
Date of final sign off	19-Jun-2023

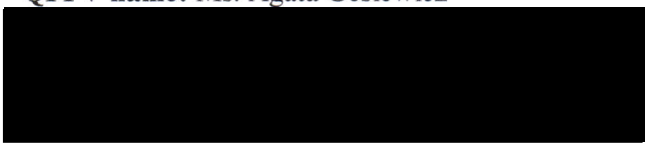
Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP: Not Applicable

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP: Not Applicable

QPPV name: Ms. Agata Gesiewicz



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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Nilotinib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors, ATC code: L01EA03
Marketing Authorisation Applicant	Accord Healthcare S.L.U. Spain Accord Healthcare Limited
Medicinal products to which this RMP refers	06
Invented name(s) in the European Economic Area (EEA) / United Kingdom (UK)	Nilotinib Accord 50 mg hard capsules Nilotinib Accord 150 mg hard capsules Nilotinib Accord 200 mg hard capsules Nilotinib 50 mg hard capsules Nilotinib 150 mg hard capsules Nilotinib 200 mg hard capsules
Marketing authorisation procedure	Centralised Procedure (H0006315) UK National (PLGB 20075/1529-1531)
Brief description of the product	**Chemical class:** Nilotinib is a member of (trifluoromethyl)benzenes, a member of pyrimidines, a member of pyridines, a member of imidazoles, a secondary amino compound and a secondary carboxamide.
	Summary of mode of action: Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such

	a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from chronic myelogenous leukaemia (CML) patients.
	Important information about its composition: Nilotinib Accord 50 mg hard capsules / Nilotinib 50 mg hard capsules One hard capsule contains 50 mg nilotinib. Excipient with known effect: One hard capsule contains 43.45 mg lactose monohydrate. Nilotinib Accord 150 mg hard capsules / Nilotinib 150 mg hard capsules One hard capsule contains 150 mg nilotinib. Excipient with known effect: One hard capsule contains 130.35 mg lactose monohydrate. Nilotinib Accord 200 mg hard capsules / Nilotinib 200 mg hard capsules One hard capsule contains 200 mg nilotinib. Excipient with known effect: One hard capsule contains 173.80 mg lactose monohydrate
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information

Indication(s) in the EEA/UK *Current*	Nilotinib Accord 50/150/200 mg hard capsules, Nilotinib 50/150/200 mg hard capsules Nilotinib Accord is indicated for the treatment of: - adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase, - adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available, - - paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.
Dosage in the EEA/UK *Current*	**Posology:** **Posology for Philadelphia chromosome positive CML adult patients** The recommended dose is: - 300 mg twice daily in newly diagnosed patients with CML in the chronic phase, - 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy. **Posology for Philadelphia chromosome positive CML paediatric patients** Dosing in paediatric patients is individualised and is based on body surface area (mg/m^2). The recommended dose of nilotinib is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Different strengths of Nilotinib Accord hard capsules can be combined to attain the desired dose.

There is no experience with treatment of paediatric patients below 2 years of age. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Table 1 Paediatric dosing scheme of nilotinib 230 mg/m^2 twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)
Up to 0.32 m^2	50 mg
0.33 – 0.54 m^2	100 mg
0.55 – 0.76 m^2	150 mg
0.77 – 0.97 m^2	200 mg
0.98 – 1.19 m^2	250 mg
1.20 – 1.41 m^2	300 mg
1.42 – 1.63 m^2	350 mg
≥1.64 m^2	400 mg

Adult Philadelphia chromosome positive CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who achieved a sustained deep molecular response (MR4.5):
Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy.

Eligible patients who discontinue nilotinib therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

	For patients who lose MR4 (MR4=BCR-ABL/ABL ≤0.01%IS) but not MMR (MMR=BCR-ABL/ABL ≤0.1%IS) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. <u>Adult Philadelphia chromosome positive CML patients in chronic phase who have achieved a sustained deep molecular response (MR 4.5) on nilotinib following prior imatinib therapy</u> Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Eligible patients who discontinue nilotinib therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Patients with confirmed loss of MR4 (MR4= BCR-ABL/ABL ≤ 0.01%IS) during the treatment-free phase (two consecutive measures separated by at least 4 weeks showing loss of MR4) or loss of major molecular response (MMR=BCR-ABL/ABL ≤ 0.1%IS) must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at either 300 mg or 400 mg twice daily.

	<u>Method of administration:</u> Nilotinib Accord should be taken twice daily approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.
Pharmaceutical form(s) and strengths *Current*	Hard Capsules 50 mg, 150 mg, 200 mg
Is the product subject to additional monitoring in the EU/UK?	No

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/UK requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

There is a European Public Assessment Report (Summary of the RMP) available for the reference product Tasigna 50/150/200 mg hard capsules (Nilotinib), published on the EMA website on 11-May-2023. There is no change proposed by the MAH in these safety concerns mentioned in Module SVIII, which are in-line with summary of safety concerns for the reference product.

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	• Significant bleeding • Severe infections • Growth retardation
Important potential risks	• Reproductive toxicity/pregnancy • Skin malignancy
Missing information	• Pediatric patients below 2 years of age

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 mentioned safety concerns.

In addition, the MAH has proposed specific adverse drug reaction follow-up forms for following risks concerning use of nilotinib and they are appended in Annex 4 of this RMP.

- Significant bleeding
- Severe infections
- Reproductive toxicity/pregnancy

Purpose: For collection of safety information to further categorise the above-mentioned safety concerns.

III.2 Additional pharmacovigilance activities

Non-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)

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 Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules (Nilotinib)

This is a summary of the risk management plan (RMP) for Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules. The RMP details important risks of Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules, how these risks can be minimised, and how more information will be obtained for Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules risks and uncertainties (missing information).

Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules should be used.

This summary of the RMP for Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules 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 Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules' RMP.

I. The medicine and what it is used for

Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules are authorised for the indications outlined below:

- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,

- adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,
- paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

It contains Nilotinib as the active substance and it is given by oral route.

Further information about the evaluation of Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules' benefits can be found in Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*link to the EPAR summary landing page*>.

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

Important risks of Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules, together with measures to minimise such risks and, 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 Nilotinib Accord 50 mg/ 150 mg/200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nilotinib Accord 50 mg/ 150 mg/200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules 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 Nilotinib Accord 50 mg/ 150 mg/ 200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules. 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	• Significant bleeding • Severe infections • Growth retardation
Important potential risks	• Reproductive toxicity/pregnancy • Skin malignancy
Missing information	• Pediatric patients below 2 years of age

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 Nilotinib Accord 50 mg/ 150 mg/200 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules.

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

There are no studies required for Nilotinib Accord 50 mg/ 100 mg/ 150 mg hard capsules and Nilotinib 50 mg/ 150 mg/ 200 mg hard capsules.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed targeted follow-up questionnaire for the following risks:

- Significant bleeding
- Severe infections
- Reproductive toxicity/pregnancy

Targeted follow-up questionnaire for Significant bleeding

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age/Age group*	Gender:	Weight (kg)	Height (cm)	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

* Neonate, Infant, Child, Adolescent, Adult or Elderly

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Administration	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						
3.						
4.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ **Yes**	○ **No**
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

Reported Cause(s) of Death[#]:	
Death date & time:	Autopsy done: ☐ YES ☐ NO
Autopsy findings:	

In case of death reported

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed	○ Unknown

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

ADDITIONAL INFORMATION:

1. Laboratory test

Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates and results.

☐ Blood tests	☐ Coagulation tests (PT/PTT, INR)
☐ Coagulation inhibitors level (antithrombin III, C protein, S protein), auto-antibodies, circulating anticoagulants	☐ Euglobulin lysis time
	☐ CT scan
☐ Chest X-ray	☐ ECG
☐ Doppler ultrasound	☐ None of the above

2. Patient History:

Does the patient have a history of any of the following? Check all that apply

☐ Ulcer	☐ Cancer
☐ Surgery	☐ Trauma
☐ Hereditary and familial disorders (i.e. hemophilia and factor deficiencies) (please specify)	☐ DIC
	☐ Platelet disorders
☐ Hemolytic disorders	☐ Varices

☐ Diverticulosis	☐ Vitamin K deficiency
☐ Bleeding disorders/abnormal coagulation tests	☐ Other relevant history (please specify)

Was the patient taking any of the following drugs at the time of the event or in the past 30 days?? Check all that apply.

☐ Oral contraceptives/HRT	☐ Antibiotics
☐ Corticosteroids	☐ Chemotherapy
☐ NSAIDs	☐ Antihypertensive agents
☐ Anticoagulants including aspirin	☐ None of the above

3. Current Medication:

1. When was last dose taken prior to event: ____AM ____PM
   amount of time between dose & food_____
2. When was the previous dose taken: ____AM ____PM
   Amount of time between dose & food_____
3. Time of last meal prior to event: _____
4. Has patient taken grapefruit juice ☐ or supplements containing grapefruit extract ☐ while taking Nilotinib?
5. Has Nilotinib been interrupted since start of therapy prior to this event? ☐ No ☐ Yes
   If yes, date:_____ Reason for change:_____
   Date resumed: _____Dose & frequency:_____
6. How long was patient on Nilotinib prior to the adverse event (total time)?
   _____

REPORTER DETAILS*:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

* Only information which is required for follow-up shall be filled. Preferred mode of communication should be asked from enquirer and accordingly above details should be filled.

Targeted follow-up questionnaire for Severe infections

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age/Age group*	Gender:	Weight (kg)	Height (cm)	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

* Neonate, Infant, Child, Adolescent, Adult or Elderly

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Administration	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						
3.						
4.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed including followings: Summary of clinical course (please include corresponding dates): Diagnosis: Treatment, including response to standard therapy	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ **Yes**	○ **No**

[redacted]

If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant
Reported Cause(s) of Death#:		
Death date & time:	Autopsy done: ☐ YES ☐ NO	
Autopsy findings:		

In case of death reported

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed	○ Unknown

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

ADDITIONAL INFORMATION:

1. **Laboratory test**

   Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates, results, and reference range and units if applicable

   ☐ Full blood count

   ☐ Culture of blood, urine and other bodily fluids (e.g. cerebrospinal, peritoneal, pleural)

   ☐ Specialized serologic tests

   ☐ PCR for infectious agent

   ☐ Imaging studies (e.g. MRI, CAT or CT)

   ☐ None of the above

2. **Relevant medical history {concurrent and pre-existing conditions)**

   (Please specify medical condition and date of onset)

   Check all that apply and please describe:

☐ Recurrent infections or chronic infections	☐ Invasive devices (e.g. on dialysis, catheter or feeding tube)
☐ Poor nutritional status (e.g. BMI < 21)	☐ Traveling or contact with contagious agents

[redacted]

☐ Corticosteroid use	☐ Weakened immune system (e.g. HIV/AIDS)
☐ Trauma with open wound or burns	☐ Chronic disease (e.g. diabetes)
☐ Peripheral vascular disease	☐ None of the above
☐ Other relevant history (please specify)	

3. Current Medication:

1. When was last dose taken prior to event: _____AM ____PM
   Amount of time between dose & food_____
2. When was the previous dose taken: ____AM ____PM
   Amount of time between dose & food_____
3. Time of last meal prior to event: _____
4. Has patient taken grapefruit juice ☐ or supplements containing grapefruit extract ☐ while taking Nilotinib?
5. Has Nilotinib been interrupted since start of therapy prior to this event? ☐ No ☐ Yes
   If yes, date: _____ Reason for change: _____
   Date resumed: _____Dose & frequency: _____
6. How long was patient on Nilotinib prior to the adverse event (total time)?
   _____
   _____

REPORTER DETAILS*:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:		Tel No.

* Only information which is required for follow-up shall be filled. Preferred mode of communication should be asked from enquirer and accordingly above details should be filled.

Targeted follow-up questionnaire for Reproductive toxicity/pregnancy

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age/Age group*	Gender:	Weight (kg)	Height (cm)	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

* Neonate, Infant, Child, Adolescent, Adult or Elderly

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Administration	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						
3.						
4.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed including followings:	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ **Yes**	○ **No**
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

Reported Cause(s) of Death[#]:	
Death date & time:	Autopsy done: ☐ YES ☐ NO
Autopsy findings:	

In case of death reported

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed	○ Unknown

ADDITIONAL INFORMATION:

Patient who took nilotinib: **Father** ☐ **Mother** ☐

1. Maternal Information

Date of Birth: _____

Method of contraception: _____

Contraception used as instructed?

☐Yes ☐No ☐Uncertain

2. Medical History (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. If none, mark as N/A)

3. Previous Obstetric History (provide details on all previous pregnancies, including termination or stillbirth)

#	Gestation Week	Outcome including any abnormalities
1.		
2.		
3.		
4.		
5.		

4. Drug Information (list all therapies taken prior to and during pregnancy)

Name of drug	Daily Dose	Date Started (dd-mmm-yyyy)	Date Stopped (dd-mmm-yyyy)	Indication	Treatment Start (week of pregnancy)	Treatment Stop (week of pregnancy)

5. Prenatal Information

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?

☐ Yes ☐ No ☐ Not Known

If Yes, please specify test date and results:

Test_____ Date_____

Result_____

6. Pregnancy Outcome

Abortion: ☐ Yes ☐ No If Yes, ☐ Therapeutic ☐ Planned ☐ Spontaneous Please specify the reason and any abnormalities (if know): _____ _____ _____ Date of abortion: _____	Delivery: ☐ Yes ☐ No If Yes, ☐ Normal ☐ Caesarean ☐ Forceps/Ventouse Maternal complications or problems related to birth: _____ _____ _____ Delivery at week: _____

7. Maternal Pregnancy Associated Events

If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form and submit immediately

8. Child Outcome

Normal ☐ Abnormal ☐ Stillbirth ☐

If any abnormalities, please specify and provide dates

_____

_____

Sex: Male ☐ Female ☐

Heigh _____cm

Wight _____kg

Head circumference _____cm

Apgar Scores:

1 minutes _____

5 minutes _____

10 minutes _____

9. Assessment of Seriousness (Of Pregnancy Outcome)

Non serious ☐	Involved prolonged inpatient hospitalization ☐	Results in persistent or significant disability/incapacity ☐
Life-threatening ☐	Mother died ☐ Date of death_____	Stillbirth/neonate died ☐ Date of death_____

Other Seriousness criteria: Congenital anomaly/birth defect ☐ Other Significant medical events ☐

10. Assessment of Causality (Of Pregnancy Outcome)

Please indicate the relationship between pregnancy outcome

Unrelated ☐ Possibly* ☐ Probably* ☐ Definitely* ☐

If any of the fields marked * have been checked, the outcome is considered to be RELATED to nilotinib.

11. Additional Information

REPORTER DETAILS*:

HCP details:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

* Only information which is required for follow-up shall be filled. Preferred mode of communication should be asked from enquirer and accordingly above details should be filled.