EU/UK Risk Management Plan
for
Apremilast Accord 10 mg film-coated tablets
Apremilast Accord 20 mg film-coated tablets
Apremilast Accord 30 mg film-coated tablets
Apremilast 10 mg film-coated tablets
Apremilast 20 mg film-coated tablets
Apremilast 30 mg film-coated tablets
(Apremilast)

RMP version to be assessed as part of this application:

RMP Version number	1.1
Data lock point for this RMP	27-Jun-2023
Date of final sign off	31-Jul-2023

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) has been updated as per the PRAC Rapporteur Risk Management Plan Assessment Report of Apremilast Accord; dated 12-Jun-2023 and Targeted follow up questionnaire has been updated in line with Otezla (apremilast) RMP published on EMA website on 29-Mar-2023.

Summary of significant changes in this RMP: Significant changes have been made in the following parts: Part I, Part III, Part VI and Part VII (Annex 4, Annex 7 and Annex 8)

Other RMP versions under evaluation**:** Not Applicable

Details of the currently approved RMP: Not Applicable

QPPV name: Ms. Agata Gesiewicz

[redacted]

[redacted]

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[redacted]

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[redacted]

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Apremilast
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, selective immunosuppressants ATC code: L04AA32
Marketing Authorisation Applicant	[redacted]
Medicinal products to which this RMP refers	06
Invented name(s) in the European Economic Area (EEA) / United Kingdom (UK)	Apremilast Accord 10 mg film-coated tablets Apremilast Accord 20 mg film-coated tablets Apremilast Accord 30 mg film-coated tablets Apremilast 10 mg film-coated tablets Apremilast 20 mg film-coated tablets Apremilast 30 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (H0006208) [redacted]
Brief description of the product	Chemical class: Apremilast is a member of the class of isoindoles that is isoindole-1,3-dione substituted at position 4 by an acetamido group and at position 1 by a 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl group.
	Summary of mode of action: Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a

	network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.
	Important information about its composition: Not Applicable
Hyperlink to the Product Information	Refer to Module 1.3.1 for Product Information
Indication(s) in the EEA/UK *Current*	Apremilast Accord 10/20/30 mg film-coated tablets Apremilast 10/20/30 mg film-coated tablets *Psoriatic arthritis:* Apremilast Accord, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. *Psoriasis:* Apremilast Accord is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

[redacted]

<table>
<tr>
<td></td>
<td>Behçet’s disease:

Apremilast Accord is indicated for the treatment of adult patients with oral ulcers associated with Behçet’s disease (BD) who are candidates for systemic therapy.</td>
</tr>
<tr>
<td>Dosage in the EEA/UK

Current</td>
<td><u>Posology:</u>

The recommended dose of apremilast is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1. Dose titration schedule

<table>
<tr><td>Day 1</td><td colspan="2">Day 2</td><td colspan="2">Day 3</td><td colspan="2">Day 4</td></tr>
<tr><td>AM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td></tr>
<tr><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td></tr>
</table>
<table>
<tr><td colspan="2">Day 5</td><td colspan="2">Day 6 & thereafter</td></tr>
<tr><td>AM</td><td>PM</td><td>AM</td><td>PM</td></tr>
<tr><td>20 mg</td><td>30 mg</td><td>30 mg</td><td>30 mg</td></tr>
</table>
If a patient misses a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment for PsA and PSOR and within the first 12 weeks of treatment for BD. If a patient shows no evidence of therapeutic benefit after this time period, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.

<u>Method of administration:</u>

Apremilast Accord is for oral use. The film-coated tablets should be swallowed whole and can be taken either with or without food.</td>
</tr>
</table>

[redacted]

Pharmaceutical form(s) and strengths *Current*	Film coated Tablets 10 mg / 20 mg / 30 mg
Is the product subject to additional monitoring in the EU/UK?	No

[redacted]

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 (RMP) available for the reference product Otezla (apremilast), published on the EMA website on 29-Mar-2023. There is no change proposed by the MAH in these safety concerns mentioned in Module SVIII, which is 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

[redacted]

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • Major adverse cardiac event (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long-term safety

[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 mentioned safety concerns.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for following risks are presented in Annex 4.

- Serious events of Hypersensitivity
- Vasculitis
- Suicidality
- Serious events of depression
- Malignancies
- Serious infections including opportunistic infections and transmission of infections through live vaccines
- MACE and tachyarrhythmia
  - Myocardial infarction
  - Cardiac arrhythmia & ECG changes
  - Cerebrovascular accident (CVA)
- Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast.

Purpose: For collection and reporting of safety information while use of apremilast.

III.2 Additional pharmacovigilance activities

None proposeds

[redacted]

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)

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 Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets (Apremilast)

This is a summary of the risk management plan (RMP) for Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets. The RMP details important risks of Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained for Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets' risks and uncertainties (missing information).

Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets should be used.

This summary of the RMP for Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 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 the future updates of RMP of Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets.

I. The medicine and what it is used for

Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets are authorised for

Psoriatic arthritis:

Apremilast Accord, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Psoriasis:

Apremilast Accord is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to

other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease:

Apremilast Accord is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

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

Further information about the evaluation of Apremilast Accord 10/20/30 mg film-coated tablets' benefits can be found in Apremilast Accord 10/20/30 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>.

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

Important risks of Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 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*.

[redacted]

If important information that may affect the safe use of Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 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 Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 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 Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 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	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • Major adverse cardiac event (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast

[redacted]

Missing information	• Long-term safety

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 Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets.

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

There are no studies required for Apremilast Accord 10/20/30 mg film-coated tablets and Apremilast 10/20/30 mg film-coated tablets.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed follow-up questionnaires for following risks:

- Serious events of Hypersensitivity
- Suicidality and Serious events of depression (Depression)
- Vasculitis
- Malignancies
- Serious infections including opportunistic infections and transmission of infections through live vaccines
- MACE and tachyarrhythmia
    - Myocardial infarction
    - Cardiac arrhythmia & ECG changes
    - Cerebrovascular accident (CVA)
- Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast.

[redacted]

Targeted follow up questionnaire for Hypersensitivity

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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]

ACTION TAKEN WITH SUSPECTED DRUGS:

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

CONCOMITANT MEDICATION (incl. herbal or self-medication, dietary supplements and OTC):

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

SPECIFIC QUESTIONS FOR EVENT HYPERSENSITIVITY:

1. Describe the temporal relationship between the event(s) and the administration of suspect drug and circumstances surrounding the hypersensitivity reaction.

   _____

   _____

   _____

2. What kind of hypersensitivity was experienced (immediate, delayed, etc.), if confirmed?

   _____

3. What was the etiology of the hypersensitivity? Please provide rationale.

   _____

   _____

4. Was the patient previously exposed to the drug or a drug from the same class?

   _____

5. Does the patient have history of hypersensitivity reactions?

   ☐ Yes ☐ No

   If yes, to which medication? _____

If yes, please describe the previous episodes. If they are drug-related, please indicate whether the patient already had a reaction to a product of the same class.

_____

_____

_____

6. What was the final diagnosis for the hypersensitivity reaction?

_____

_____

7. Please check the types of specific symptoms observed:

☐ Fever, Chills	Describe:
☐ Urticaria	Describe:
☐ Angioedema	Describe:
☐ Dizziness	
☐ Dyspnea	
☐ Bronchospasm	
☐ Tachycardia	Indicate Heart Rate (HR):
☐ Hypotension	Indicate systolic/diastolic BP:
☐ Shock	Describe:
☐ Renal dysfunction	Indicate laboratory values:
☐ Hepatic dysfunction	Indicate laboratory values:
☐ Pneumonitis/lnterstitial lung disease	Describe:
☐ Others	Describe:

8. Please describe the kind of treatment administered (type, dose and route of administration).

_____

9. What was the outcome of the event?

_____

10. Has this patient subsequently been re-exposed to apremilast?

☐ Yes ☐ No

11. If yes to above re-exposure question, did the event re-appear?

☐ Yes ☐ No

12. If yes (event re-appeared), at which dose?

☐ Same ☐ Different

If the dose was different than before, please indicate:

_____

13. If this patient was subsequently re-exposed was there any prophylaxis administered?

☐ Yes ☐ No

If yes, what kind of prophylaxis?

_____

14. Has there been any recent change of any of these treatments?

☐ Yes ☐ No

If yes, please describe:

_____

15. Has any diagnostic workup been performed for this event?

☐ Yes ☐ No

If yes, please describe:

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

Targeted follow up questionnaire for Suicidality and Serious events of depression

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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	○ Life Threatening	○ Congenital Abnormality
○ Involved/Prolonged Hospitalisation	○ Disability/Incapacity	○ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

[redacted]

○ 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.					

SPECIFIC QUESTIONS FOR EVENTS SUICIDALITY AND DEPRESSION:

1. Did the patient have any previous episodes of suicide attempts or ideation? ☐Yes ☐
   If yes, please provide details.

   _____

   _____

2. Has the patient been hospitalised for similar events? ☐Yes ☐No
   If yes, please provide details.

   _____

   _____

3. Does the patient have a history of depression? ☐Yes ☐No
   If yes, provide information including start date of depression, treatments for depression.

   _____

   _____

4. If the patient has a history of depression, did the depression recently worsen?
   ☐Yes ☐No
   if yes, please provide details.

   _____

   _____

5. Is the patient receiving any medications other than Apremilast which have been associated with suicide attempts or ideation?
   ☐Yes ☐No
   if yes, please provide details.

[redacted]

_____

_____

6. Does the patient abuse alcohol or drugs?

   ☐Yes ☐No

   If yes, please provide details.

   _____

   _____

7. Did the patient have any recent change in his/her social circumstances (job loss, family death, divorce, etc.)?

   ☐Yes ☐No

   if yes, please explain.

   _____

   _____

8. Please provide causality for suicidal ideation/attempt:

   ☐ Related to Apremilast ☐ Not related to Apremilast ☐ Unknown

   ☐ Other: please specify: _____

Treatment details:

9. Provide details of the treatment given for this episode:

   _____

   _____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Targeted follow up questionnaire for Vasculitis

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

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

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

2.					
3.					

SPECIFIC QUESTIONS FOR EVENT VASCULITIS:

SIGNS AND SYMPTOMS

1. Indicate type of vasculitis:

☐ small vessel ☐ medium vessel ☐ large vessel

Please provide details:

_____

_____

2. Please describe presenting signs and symptoms (cutaneous or systemic manifestations, visceral involvement):

_____

_____

3. Please provide description of cutaneous manifestations with extent/severity and localization of areas:

_____

_____

4. Were there any associated infections around this presentation?

☐ Yes

☐ No

If yes, please specify type of infection, date and treatment receive:

_____

_____

DRUG INFORMATION/DECHALLENGE/RECHALLENGE

1. Provide time to onset of this event (after start of Apremilast or duration of therapy). When did the vasculitis appear?

_____

_____

2. What action was taken with Apremilast due to this event?

[redacted]

☐ None
☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and dose: _____

3. If Apremilast was discontinued, did the lesion(s) abate after discontinuation?

☐ Yes ☐ No

4. Was Apremilast re-introduced?

☐ Yes ☐No

If yes, did the lesion(s) re-occur after re-introduction? ☐Yes ☐No

Provide Apremilast restart date and dosing: _____

5. Was the patient receiving treatment for vasculitis when Apremilast was resumed?

☐Yes ☐No

If yes, indicate the drug name with therapy dates:

_____

_____

6 Please provide causality for Vasculitis:

☐ Related to Apremilast ☐ Not related to Apremilast ☐ Unknown
☐ Other: please specify: _____

WORK UP

1. Provide full biopsy report and/or supporting documentation for the diagnosis of vasculitis.

_____

2. Provide CBC with eosinophils.

_____

_____

3. Include any results of serologic studies, blood cultures, sedimentation rate, chemistry panel, ANA, ANCA, rheumatoid factor, IgA anti phospholipid antibodies, total hemolytic complement, C3/C4, hepatitis panel, cryoglobulins, as appropriate.

_____

[redacted]

_____

4. Imaging studies: chest x-ray, visceral angiography as appropriate.

_____

5. Provide status of underlying disease around onset of this event.

_____

_____

TREATMENT

1. Please provide treatment/intervention for the vasculitis. Specify drug names, route (oral, topical, IV) and administration dates.

_____

_____

2. Was a specialist consulted for further investigation? If so, please provide those findings.

_____

_____

MEDICAL HISTORY

1. Has patient had similar episodes of vasculitis before?

_____

_____

2. Please indicate whether or not the patient had a history of the following:

Medical history	**Yes**	**No**	**Specify**
Rheumatoid arthritis	☐	☐	
SLE	☐	☐	
Sjogren syndrome	☐	☐	
Other Inflammatory disease	☐	☐	If yes, specify:
Past hypersensitivity reaction	☐	☐	
Intravenous drug use	☐	☐	

Blood transfusion	☐	☐	
Travel history	☐	☐	If yes, specify:
Food or food additives reaction	☐	☐	
Henoch-Schonlein purpura	☐	☐	
Hepatitis	☐	☐	
HIV	☐	☐	
Other Infections	☐	☐	If yes, specify:

REPORTER DETAILS:

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

[redacted]

Targeted follow up questionnaire for Malignancies

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

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.					

SPECIFIC QUESTIONS FOR EVENT MALIGNANCIES:

1. Dates of treatment in regard to the event:

_____

2. Dates of the underlying disease's diagnosis:

_____

3. Is this the first time that the patient has been treated with Apremilast?

☐ Yes

☐ No

☐ If no, please provide dates:

4. Previous history of malignancies (personal/familial) with estimated dates:

_____

_____

5. Underlying medical history and concomitant diseases:

_____

_____

6. Any previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose)?

_____

_____

_____

7. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies:

_____

_____

8. Tobacco, alcohol abuse:

_____

_____

9. Date of diagnosis of malignancy and date of first clinical symptoms:

_____

10. Full biopsy reports with exact stage. If not available, please provide the detailed results:

_____

_____

_____

11. Treatment of malignancy, provide details:

_____

_____

RISK FACTORS FOR SPECIFIC TYPES OF CANCER:

Lung Cancer: ☐ Smoking history - length of time, number of cigarettes/days, age at starting, gender, product smoked and depth of inhalation ☐ Pre-existing pulmonary disease ☐ Family history of lung cancer ☐ Arsenic, asbestos, nickel, pesticides, radon or chromates exposure	**Lymphoma:** ☐ Medical conditions that compromise the immune system - HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant ☐ Infection with HIV, Epstein-Barr virus, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma
Thyroid Cancer: ☐ Personal or family history of thyroid and/or autoimmune diseases hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves' disease ☐ Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis. ☐ Living in iodine deficient area	**Breast Cancer:** ☐ Receptor status of the tumor - ER, PR, Her2/neu ☐ Age at onset of menses and age of menopause ☐ Number of pregnancies and age at first birth ☐ History of breastfeeding children ☐ Use of oral contraceptives or hormone replacement therapy ☐ Obesity ☐ Ethnic group, economic status and dietary iodine deficiency

[redacted]

Ovarian Cancer: ☐ Number of pregnancies and childbearing status ☐ History of hormone replacement therapy ☐ History of breast cancer	**Uterine Cancer:** ☐ Age at onset of menses and age of menopause ☐ Number of pregnancies ☐ Use of oral contraceptives ☐ Obesity
Colon Cancer: ☐ Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer ☐ Diet high in red meat and animal fat, refined carbohydrates, low- fiber diet, and low overall intake of fruits and vegetables ☐ Obesity and sedentary habits ☐ Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement	**Anorectal Cancer:** ☐ History of infection with human papillomavirus, chronic fistulas, irradiated anal skin, leukoplakia lymphogranuloma venereum, condyloma acuminatum ☐HIV status **Oesophageal Cancer:** ☐ Genetic causes - tylosis (hyperkeratosis palmaris et plantaris) ☐ Alcohol use/smoking ☐ History of chronic or acute inflammation (e.g. GERO, Barrett's esophagus, caustic ingestion)Achalasia (oesophageal motility disorder) ☐ Human papilloma virus ☐ Sclerotherapy ☐ Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)
Gastric Cancer: ☐ Diet rich in pickled vegetables, salted fish, salt, and smoked meats ☐ Helicobacter pylori infection ☐ Obesity ☐ Previous gastric surgery ☐ Pernicious anemia, adenomatous polyps, gastric ulcer ☐ Chronic atrophic gastritis ☐ Radiation exposure	**Liver cancer:** ☐ History of cirrhosis (including alcoholic, biliary cirrhosis), other chrome liver dysfunction ☐ Alcohol use ☐ Hepatitis B, C ☐ Hemochromatosis ☐ Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)
Pancreatic Cancer ☐ Smoking ☐ Obesity ☐ Diet (red meat) ☐ History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women) ☐ Inherited predisposition hereditary pancreatitis, familial adenomatous poliposis)	**Renal Cancer (renal cell carcinoma** ☐ Smoking ☐ Obesity ☐ Hypertension ☐ Phenacetin-containing analgesics taken in large amounts ☐ History of renal transplantation: ☐ Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products

[redacted]

	☐ Inherited VHL disease (van Hippel-Lindau disease), Adult polycystic kidney disease, Tuberous sclerosis
Bladder Cancer: ☐ Smoking ☐ Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles ☐ Occupation - painting, driving trucks, and working with metal ☐ Prior spinal cord injuries with long-term indwelling catheters	**Prostate Cancer** ☐ Ethnic group ☐ History of high-grade prostatic intraepithelial neoplasia (PIN) ☐ Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes ☐ Testosterone level ☐ History of sexually transmitted diseases ☐ History of vasectomy ☐ History of exposure to cadmium ☐ History of genitor-urinary infections
Head and Neck Cancer ☐ Smoking and alcohol use ☐ Prolonged sun exposure ☐ Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV) ☐ Ethnic group ☐ History of poor oral hygiene and/or poor nutrition ☐ Exposure to asbestos, wood dust, paint fumes or chemicals ☐ History of Gastroesophageal reflux disease (GERD) or Laryngopharyngeal reflux disease (LPRD)	**Brain Tumors (gliomas and menigiomas)** ☐ Exposure to radiation ☐ Exposure to vinyl chloride, Pesticides ☐ Immune system disorders ☐ Hormone replacement therapy **Nasal and Paranasal Sinus Cancer:** ☐ Woodworking, any dust/flour chronic exposure ☐ History of Infection with human papillomavirus (HPV) ☐ Smoking
Larynx Cancer ☐ Smoking history, alcohol use ☐ Asbestos exposure ☐ Any activity requiring loud speech, exposure to sudden and frequent temperature changes ☐ Frequent hoarseness, frequent and persistent cough ☐ Persistently swollen neck glands ☐ Tonsillectomy and laryngeal surgery	**Mouth and Oropharyngeal Cancer** ☐ Smoking ☐ Alcohol use ☐ History of poor oral hygiene ☐ Chronic mucosal/gum irritation I ill-fitting dentures ☐ Betel-Nut Chewing {Indian populations) ☐ History of syphilis or viral infections ☐ Impaired immunity - AIDS, transplant with anti-rejection drugs ☐ Precancerous mouth plaques - Leukoplakia or erythroplasia ☐ History of cancer of the aero-digestive tract
Melanoma: ☐ History of prolonged sun exposure (UV radiation) - severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths	

☐ History of living close to equator or at high elevation
☐ History of skin conditions - Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
☐ Skin type - fair (pale) skin - burns easily, freckles
☐ History of prolonged sun exposure (UV radiation)
☐ Eye colour - blue, green or grey, Hair colour - blond or red
☐ Use of medication causing sensitivity to sun - antibiotics, hormones, antidepressants,
☐ Immune system depression - AIDS, leukemias
☐ Exposure to arsenic, coal tar or creosote
☐ For eye localization: History of oculodermal melanocytosis or Dysplastic nevus syndrome
☐ Ethnic group

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

Targeted follow up questionnaire for Serious infections

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

ACTION TAKEN WITH SUSPECTED DRUGS:

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

[redacted]

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

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

SPECIFIC QUESTIONS FOR EVENT SERIOUS INFECTIONS INCLUDING OPPORTUNISTIC INFECTIONS AND TRANSMISSION OF INFECTIONS THROUGH LIVE VACCINES:

1. Please provide the type and source of infection:

_____

2. Does the patient have a history of recurrent infection?

☐ Yes ☐ No

If yes, please explain:

_____

_____

3. Please provide the type and the stage of the patient's disease (specify) at the time of the onset of the event.:

_____

_____

4. Any history of bone marrow involvement, bone marrow transplantation or radiotherapy? If so, please provide approximate dates:

_____

_____

5. Please name any underlying condition(s) that may be relevant to the reported event, e.g. stage of disease, previous history of infection, neutropenia, exposure to monoclonal antibodies:

_____

_____

6. Please indicate one or more of the following:

☐ De novo infection ☐ Recurrent infection ☐ Relapse

7. If the patient was on infection prophylaxis, did he/she receive colony stimulating factors, antibiotics, etc.?

[redacted]

☐ Yes ☐ No

If yes, please provide type and dates_____

8. Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Range w/ Units	Baseline / Date (prior to Apremilast)	Worst/ Date	Recovery/ Date
WBC				
ANC				

9. Please provide relevant culture/serology results with dates:

_____

_____

10. Please provide any additional diagnostic test results/ laboratory values (Chest x-ray, CT scan, ultrasound, CBC, haemoglobin, RBC) including baseline, event onset and recovery values, with dates, for the reported event.

_____

_____

11. What treatments were given for the infection? Please include dates.

_____

_____

OPPORTUNISTIC INFECTIONS (only if appropriate):

1. Any suspicion or evidence of the following types of infections (incomplete list):

Viral: ☐ Epstein Barr virus (EBV) ☐ Hepatitis B (HBV) ☐ Cytomegalovirus (CMV) ☐ Herpes simplex (HSV) ☐ Varicella zoster virus (VZV) ☐ Progressive multifocal leukoencephalopathy (PML)	**Protozoa**l: ☐ Pneumocystis carinii (PCP) ☐ Toxoplasmosis **Fungal**: ☐ Candidiasis ☐ Aspergillosis ☐ Histoplasmosis ☐ Cryptococcosis
Malignancies: ☐ Kaposi sarcoma (KS)	**Bacterial** ☐ Tuberculosis (TBC) ☐ Mycobacterium avium (MAI) ☐ Salmonellosis

2. If the answer to any of the above is yes, please indicate whether this diagnosis has been confirmed, and if so, how?

_____

_____

[redacted]

3. In case of suspected EBV and HBV, please provide test results in the table below

Test	Baseline/ Date	Worst/ Date	Recovery/ Date
EBV viral load (PCR)			
EBER (Epstein Barr virus encoded RNA)			
HBsAg			
HBs Ab			
HBc Ab			
HBV DNA			
Hepatitis A			
Hepatitis C			
Hepatitis D			
Hepatitis E			
Transaminase			
Bilirubin			

4. Is there a history of hepatitis or does the event represent a new infection?

_____

SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCI/TIS (only if appropriate):

1. Please provide the starting point of the soft tissue infection

_____

2. Please indicate if local precipitating event(s) causing NF has(ve) been identified at the starting site of occurrence and which ones (e.g. traumatic including surgery, minor invasive procedures [e.g. joint aspirations], and penetrating injuries [e.g. insect and animal bites] and nontraumatic including soft tissue bums)

_____

_____

3. If the suspect drug is an injectable form, please specify the route of administration.

☐ SC
☐ IV

4. If the route of administration of the suspect drug was SC, please specify if the starting point of the soft tissue infection was at the injection site.

_____

_____

5. Please specify if any of the below risk factor has been identified,

☐ Diabetes ☐ Chronic disease, if yes, specify: ☐ Immunosuppressive drugs (including corticosteroids) If yes, specify: _____ ☐ Malnutrition ☐ Age > 60 years ☐ Peripheral vascular disease ☐ Alcohol /drug abuse, if yes, specify:	☐ Renal failure ☐ Obesity ☐ Recent childbirth ☐ Recent infection with rash (e.g. varicella) ☐ Recent stay in health care facility ☐ Recent dental work ☐ Others, if yes, specify

6. Please provide the identified infectious causative pathogen and source of identification (e.g. skin or blood culture/serology results with dates):

_____

_____

7. Please provide any additional diagnostic test results if available (eg scan; MRI; skin biopsy; muscle biopsy)

_____

_____

8. Please provide additional lab data including:

Test	**Range w/ Units**	**Baseline/ Date (prior to Apremilast)**	**Worst/ Date**	**Recovery/ Date**
CPK MM				
CPK				
lactate				
BUN				
Creatinine				
Glucose				
INR				
PT				
D- Dimer				
Serum C-reactive Protein				

9. Please provide treatment of the infection including local procedures (e.g. surgery)

_____

[redacted]

10. Please provide post-surgery pathology results including also cultures from deep specimen samples during the intervention:

_____

_____

11. Patient's hobbies (e.g. fishing, weightlifting/heavy workout/gardening):

_____

_____

REPORTER DETAILS:

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

Targeted follow up questionnaire for MACE and tachyarrhythmia (Cardiac Arrythmia and ECG Changes)

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

ACTION TAKEN WITH SUSPECTED DRUGS:

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

[redacted]

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

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

SPECIFIC QUESTIONS FOR EVENT CARDIAC ARRYTHMIA AND ECG CHANGES:

1.Type of arrhythmia/ECG change:

_____

2.Clinical signs and symptoms, if present (if none please state):

_____

_____

3.Start date (dd/mm/yyyy): __/__/____ Stop date (dd/mm/yyyy): __/__/____

4.Does this patient have a relevant cardiac history?

☐ Yes ☐ No

If yes, please specify in box below.

Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardiorespiratory problems)?

Medical History (Diagnosis)	**Onset Date /Duration**

5. Please provide the available results of the diagnostic workup (use separate sheet if necessary)

Test	**Baseline**		**Event Onset/Worst**		**Recovery/ Latest**	
	Date	**Results**	**Date**	**Results**	**Date**	**Results**
EKG findings						
Echocardiogram						
Chest x-ray						

Holter, Stress Test						

6. Please provide the available results of the diagnostic workup (always ask for the results of serum potassium and magnesium studies - use separate sheet if necessary)

Laboratory Testing	Reference Range	At Baseline		At Event Onset/Worst		Recovery/Latest	
		Date	Value	Date	Value	Date	Value
CPK CPK-MB							
Troponin							
RBC							
Hemoglobin							
Metabolic Panel (specify)							
Serum potassium							
Serum magnesium							
Phosphorus							
Calcium							
Uric acid							
Creatinine							
BUN							

7. Please describe specific treatments and interventions of the arrhythmia:

_____

8. Please mention cardiovascular diagnosis other than arrhythmia based on ECG changes:

_____

_____

9. Please provide causality for arrhythmia/ECG changes:
   - ☐ Related to Apremilast
   - ☐ Not related to Apremilast
   - ☐ Other: please specify _____
   - ☐ Unknown

[redacted]

REPORTER DETAILS:

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

Targeted follow up questionnaire for Myocardial Infarction

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

ACTION TAKEN WITH SUSPECTED DRUGS:

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

[redacted]

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

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

SPECIFIC QUESTIONS FOR EVENT MYOCARDIAL INFARCTION:

1. Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

2. Please provide any risk factors for the myocardial infarction (hyperlipidaemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary lifestyle, immobility, dehydration, etc.).

3. Please provide the following laboratory data: serial CPK and MB, troponin, BNP, Blood cell counts, Hgb, Hct, electrolytes including Mg, and Ca. Please include baseline, worst, and recovery values and dates drawn.

4. Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterization, if available.

5. Please provide the treatment and interventions that were administered due to the myocardial infarction.

6. Please provide RELEVANT concomitant medications including indications, dosage, and therapy dates. Please include erythropoietin and thromboprophylactic medications and others as appropriate.

_____

7. Please provide concurrent events/circumstances surrounding the MI.

_____

_____

8. Did the patient have a history of chest pain?

_____

9. Was the patient receiving thromboprophylaxis? If yes, which type and dose?

_____

10. Did the patient have a history of thromboembolic events? If yes, please specify type.

_____

_____

REPORTER DETAILS:

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

[redacted]

Targeted follow up questionnaire for Cerebrovascular Accident (CVA)

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

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

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

SUSPECTED DRUG(S):

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

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

ACTION TAKEN WITH SUSPECTED DRUGS:

[redacted]

○ 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.					

Specific questionnaires for Cerebrovascular Accident (CVA)

1. Please characterize the cerebrovascular accident ☐ ischemic ☐ hemorrhagic ☐ unknown
2. Please provide details surrounding the CVA (shock, infection, thromboembolic event, status of underlying cardiac disease, etc)

   _____

   _____
3. Please provide CBB and blood pressure at baseline (prior to receiving Apremilast therapy) and at time of CVA

   _____

   _____
4. Please provide relevant diagnostic imaging results (EEG, CT, MRI, PET, etc) or other (Doppler, EKG) including dates and results.

Test	Date (dd/mmm/yyyy)	Results
Electroencephalogram (EEG)		
Computed Tomography (CT) scan		
Magnetic Resonance Imaging (MRI)		
Positron Emission Tomography (PET) scan		
Others (specify))		

5. Please provide pertinent medical including risk factors

History/Risk Factors	Yes	No	Comments
Previous CVA	☐	☐	
Atrial fibrillation	☐	☐	
Arrhythmia, specify _____	☐	☐	
Renal disease	☐	☐	
Hypertension	☐	☐	

[redacted]

History/Risk Factors	Yes	No	Comments
Diabetes	☐	☐	
High cholesterol	☐	☐	
Tobacco use	☐	☐	
Substance abuse	☐	☐	
Others (specify) _____	☐	☐	

6. Please clarify if the patient was using or was exposed to any anticoagulants/thromboprophylaxis prior to CVA

   ☐ Yes ☐ No ☐ Unknown

   If yes, please provide specific anticoagulants/thromboprophylaxis used prior to CVA and therapy dates.

Drug Name	Indication	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)

7. Please provide concomitant drugs including drug names, indications and theapy dates.

   ☐ None ☐ Unknown

Drug Name	Indication	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)

8. Please provide the treatment/intervention measures:

   _____

   _____

9. Please provide causality for CVA:
   - ☐ Related to Apremilast
   - ☐ Not related to Apremilast
   - ☐ Other: please specify
   - ☐ Unknown

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

Initial Pregnancy Questionnaire (Mother)

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

DETAILS OF MOTHER (PATIENT):

Mother's Initials	**Date of birth** (if permitted to provide by local laws) (dd/mmm/yyyy)	**Date of last menstrual period:** (dd/mmm/yyyy)
Age:_____years Number of fetuses _____	**Estimated date of delivery:** (dd/mmm/yyyy)	

Relevant Laboratory Tests & Procedures

Test Name	Test Date (dd/mmm/yyyy)	Test Results

MOTHER PRENATAL MEDICATION HISTORY:

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.]) and vaccines, taken by the mother within 3 months prior to or pregnancy.

Name of drug/brand name	**Dose**	**Route of administration**	**Frequency**	**Start date of drug**	**Stop date of drug**	**Weeks of pregnancy when drug taken (e.g. week 28-32)**	**Indication for treatment**
Resumed (if applicable)							
Batch number _____ ☐ batch number not known							

List of any other medications used within 3 months prior to or during the pregnancy:

Medications /Drugs	**Indication**	**Dose**	**Route of administration**	**Frequency**	**Start date of drug**	**Stop date of drug**

PREGNANCY COMPLICATION AND ADVERSE EVENT INFORMATION:

If the mother experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, palcenta previa, etc.)

Pregnancy complication or adverse event	**Date the complications or event started (dd/mmm/yyyy)**	**Date the complication or event resolved (dd/mmm/yyyy)**	**Outcome**

MOTHER RELEVANT MEDICAL HISTORY:

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐difficulty conceiving ☐ asthma ☐ thyroid dysfunction

☐ other_____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.

MOTHER PREVIOUS OBSTETRICAL (PREGNANCY) HISTORY:

Please provide the number of pregnancies after treatment with an Apremilast was initiated. Include the pregnancy outcome for each of these pregnancies and any additional relevant details.

[redacted]

☐ Normal healthy baby_____ ☐ Miscarriage_____ ☐ Stillbirth_____ ☐ Abortion (induced for medical reason) _____ _____ ☐ Outcome unknown _____	☐ Baby with birth defect_____ ☐ Abortion (induced for non-medical [voluntary] reason): _____ _____ ☐ Other (specify outcome) or any significant additional information: _____ _____

MOTHER CURRENT PREGNANCY OUTCOME (IF APPLICABLE):

- Date of pregnancy ended _____
- Weeks of pregnancy at delivery _____ Weeks
  (or outcome was a loss of pregnancy)
- Pregnancy Outcome (please check the appropriate box below):
  - ☐ Live birth
    - Number of infants: _____
    - Gender: ☐Male ☐ Female
    - Length _____ Cm/Inches
    - Head circumference _____ Cm/Inches
    - Birth Weight _____ gram/lb
  - ☐ Pregnancy loss (miscarriage)
  - ☐ Stillbirth
  - ☐ Termination
    - ☐ Due to health issue (mother or baby)
    - ☐ For voluntary reason
    - ☐ Other (please specify):
  - Normal pregnancy (healthy new born) ☐

Did the baby have any complications/medica problems/congenital anomalies (borht defects)? ☐ Yes ☐ No
If yes please provide specific information on the medical problem:

Please confirm if there were any tests done or results given for the baby/fetus? ☐ Yes ☐ No If yes, please provide the details below.
Additional information on pregnancy outcome and/or test/results.

REPORTER DETAILS:

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

[redacted]

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

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

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued Apremilast or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/ Drugs	Dose	Route of administration	Frequency	Date Drug Started (dd/mm/yyyy)	Date Drug Stopped (dd/mm/yyyy)	Indication

MOTHER PREGNANCY COMPLICATIONS AND/OR ADVERSE EVENT INFORMATION NOT PREVIOUSLY REPORTED:

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yyyy)	Date the Complication or Event Resolved (dd/mm/yyyy)	Outcome (e.g.: resolved, not resolved, unknown, other, etc.)

MOTHER CURRENT PREGNANCY OUTCOME (IF APPLICABLE):

Date pregnancy ended_____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy: _____(Weeks)

Pregnancy Outcome (please check the appropriate box below):

☐ Live birth

☐Number of infants: _____ (1: single, 2: twins, etc) (For multiple birth, provide information for each infant in the additional information text below)

☐ Gender: ☐ Male ☐ Female

☐ Length _____ Cm/Inches

☐ Head circumference_____ (cm/inches)

☐ Birth Weight _____ (gram/lb)

☐ Pregnancy loss (miscarriage)

☐ Stillbirth

☐ Termination

☐ Due to health issue (mother or baby)

☐ Voluntary reason

☐ Other (please specify):

Did the baby have any complications/medical problems/congenital anomalies (birth defects)?

☐ Yes ☐ No

If yes, please provide specific information below.

Additional Information on pregnancy outcome:

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

SIX AND TWELVE-MONTH INFANT QUESTIONNAIRE

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

INFANT HEALTHCARE PROVIDER (HCP) INFORMATION:

May Accord contact the HCP for medical information regarding your child? ☐ Yes ☐ No

Name _____Phone _____ Fax_____

Email Address _____ City _____

State/Province_____ Zip/Postal code _____ Country_____

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child):

Medication/ Drugs	Dose	Route of administration	Frequency	Drug start date dd/mmm/yyyy	Drug stop date dd/mmm/yyyy	Indication

Has the infant had any abnormal screening tests? ☐ Yes ☐No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?
☐ Yes ☐ No If yes, please explain:

Has the infant had any illnesses or persistent health problems?

☐ Yes ☐ No If yes, please explain:

[redacted]

REPORTER DETAILS:

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