The Prescriber's Guide

For

Cidofovir Exposure Study

Sponsors

Tillomed Laboratories Limited

Tillomed Pharma GmbH

Laboratorios Tillomed Spain SLU

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Prescribers' Guide

In this document, the following terminology is used*:*

"**Cidofovir**" means Tillomed's Cidofovir 75 mg/mL concentrate for solution for intravenous infusion.

"**EMA**" means European Medicines Agency.

"**GDPR**" means the General Data Protection Regulation.

"**Guardian**" means the person who is legally responsible for the Patient, where the Patient is under 18 or lacks legal capacity to consent to participation in the Study.

"**Informed Consent Form"** or **"ICF**" means the form of the same name attached to the Patient Information Sheet.

"**Lead Sponsor**" means Tillomed Laboratories Limited.

"**Patient**" means the person prescribed Cidofovir and taking part in the Study.

"**Patient Information Sheet**" means the document of the same name.

"**Prescriber**" means the doctor or pharmacist who is treating the Patient.

"**Registry**" means the Cidofovir Exposure Registry which is a database for collecting and storing Patients' medical and other information in connection with treatment using Cidofovir for use in medical research. The Registry's URL is http://www.cidofovir.com

"**Sponsors**" means Tillomed Laboratories Limited, Tillomed Pharma GmbH and Laboratorios Tillomed Spain SLU which are jointly conducting and funding the Study at the direction of the EMA.

"**Study**" means a non-interventional study to monitor what type of Patients are treated with Cidofovir, what it is used for, and to compare patterns and rates of adverse reactions between Patients who are prescribed it for its "on label" (licensed) use and those who are prescribed it to treat an "off label" (unlicensed) symptom. The Study is being undertaken in the United Kingdom, Germany, Belgium and Spain.

"**Unique Study Reference Number**" means a unique number assigned to each Patient for the purposes of the Study only.

"**You**" means the Prescriber.

1. Pre-Enrolment Activities

1.1 Training on the Cidofovir Exposure Study documents

Before initiating the enrolment process, please read the Cidofovir Exposure Study Synopsis where the Study objectives are set out.

As the Study requires recording of medical information in a web based electronic data capture (EDC) system (Registry), please familiarise yourself with the electronic baseline data form and follow-up data form in the Registry.

Training on the key aspects of the Study will be provided to You by the Cidofovir representative, if required.

1.2 Eligibility criteria

All Patients who are treated with Cidofovir and who sign the Patient Information Sheet and Informed Consent Form (or have them signed by a Guardian) are eligible for enrolment in the Study.

There is no limit to the number of Patients you can enrol in the Study.

1.3 Patient Information Sheet and Informed Consent Form

If You have Patients currently receiving, or You identify a Patient requiring, Cidofovir treatment, please inform the Patient about the Study and offer him/her the Patient Information Sheet and attached Informed Consent Form (ICF).

You may offer help to the Patient (and a family member or Guardian) to understand the Patient Information Sheet and ICF, and any other relevant information regarding the Study. Any questions that the Patient may have regarding his/her participation must be answered to his/her satisfaction.

If the Patient (or his/her Guardian on his/her behalf) agrees to participate in the Study, the Patient (or Guardian, if applicable) must sign at the bottom of every page of the Patient Information Sheet and ICF and in the relevant box on page 8.

A copy of the signed Patient Information Sheet and ICF must be uploaded to the Registry.

You must give the Patient (or Guardian) a copy of the signed Patient Information Sheet and ICF.

The original signed Patient Information Sheet and ICF must be kept by You with the Patient's other medical records.

If the Patient is a minor, consent is given by their Guardian, and they celebrate their 18th birthday during the course of the Study, it will be necessary to have the Patient sign a new Patient Information Sheet and Informed Consent Form themselves before further follow-up forms are completed.

1.4 Assignment of Unique Study Reference Numbers to Patients

When the signed Patient Information Sheet and ICF are uploaded to the Registry, You will be allotted a Unique Study Reference Number for that Patient. The Unique Study Reference Number will link the electronic baseline data form and the follow-up forms for each Patient. It will also be the way in which Patients are identified in correspondence or emails, together with their gender and year of birth as a cross check.

You will be able to access completed baseline data forms and follow up forms for your Patients through their Unique Study Reference Numbers.

2. Patient Information

Baseline data form

The information collected at enrolment will be captured in the baseline data form and, if either some or all of it is not available at the time of enrolment, it can be captured in the follow-up form.

The data to be captured in the baseline data form at the time of enrolment are listed below:

- **Confirmation of informed consent and Patient eligibility**
- **Demographic data**
- **Medical history** (if any significant/major illnesses, medical conditions or surgeries are on-going, leave stop date blank and tick “on-going”)
- **Concomitant medications** (if the medication is on-going, leave stop date blank and tick “on-going”)
- **Laboratory investigations** (if relevant data is not available at the time of completion of the baseline data form, it must be included on a follow up form)
- **Treatment initiation details**
- **Prescriber’s sign off**: You are required to digitally sign the electronic form after checking the information obtained from the Patient during the baseline visit has been entered correctly.

3. Follow-Up Information

All serious adverse events (SAEs), must be notified to the Lead Sponsor within 24 hours of appearance as set out in the section "*Communication with Lead Sponsor*" You must refer to the Patient by their Unique Study Reference Number and their year of birth and gender only. You must not refer to the Patient's name or any other identifying details.

- In addition, all adverse events that occur during the course of the Study must be documented in a follow-up form with special attention to renal events (including nephrotoxicity including Fanconi syndrome and renal failure), carcinogenic events and SAEs if any.

The following details must be recorded for all adverse events:

- ✓ Event term
- ✓ Start date and stop date (or if on-going, leave stop date blank)
- ✓ Whether the event was a SAE
- ✓ Whether any concomitant medication was given
- ✓ Record the Cidofovir treatment status:
  - Mark '0' if treatment is on-going
  - Mark '1' if treatment is temporarily interrupted
  - Mark '2' if treatment has been permanently withdrawn
- ✓ Record the adverse event outcome:
  - Mark '0' if resolved
  - Mark '1' if resolved with sequelae
  - Mark '2' if not resolved
- ✓ Record the relationship of the adverse event to Cidofovir:
  - Mark '0' if it is definitely related
  - Mark '1' if it is probably related
  - Mark '2' if it is possibly related
  - Mark '3' if it is unlikely to be related
  - Mark '4' if it is not related
  - Mark '5' if it is not assessable

- **Results of laboratory investigations** (include relevant data if not available at the time of completion of the baseline data form and updates to baseline data)
- **Patient outcome**
- **Treatment details**: please record if treatment regimen has been changed since last visit. Subsequently, the final treatment regimen is also to be recorded.
- **Medical history.** (if any significant/major illnesses, medical conditions or surgeries are on-going, leave stop date blank and tick “on-going”)
- **Concomitant medications**: (if the medication is ongoing, leave stop date blank and tick “on-going”).
- **Prescriber’s sign off**: You are required to digitally sign the electronic form after checking the information obtained from the Patient during the follow-up visit has been entered correctly.

Schedule of Events

Study Visits	Baseline Visit	Follow-up Visit*
Parameters		
Informed consent and eligibility	**X**	
Generate Unique Study Reference Number	**X**	
Demographic Data	**X**	
Medical history	**X**	**X**
Concomitant medication	**X**	**X**
Laboratory investigations	**X**	**X**
Cidofovir treatment details**	**X**	**X**
Adverse Events		**X**
Patient Outcome		**X**

*__Follow–up visit(s) can be any time after the baseline visit__
__**Includes recording of indication, dose, frequency, route of administration and duration of treatment__

Data collection for centres in Germany

If You are a Prescriber in Germany, you must comply with the German Medicines Act as follows:

- **Patients treated in line with approved label** - the baseline data and the follow-up data must be recorded in the baseline data form and follow-up form.

- **Patients treated for off-label indication**: the ICF, eligibility criteria, demographic data, treatment regimen and indication are to be captured as baseline details in the baseline data form. No details are to be recorded in the follow-up form for such Patients.

4. Communication with Lead Sponsor

The Study representative from the Lead Sponsor will liaise with You about requirements or clarifications during the Study.

The Study representative will contact You periodically to follow up adverse events and the outcome of treatment.

Contact details for Lead Sponsor:

Address 220 Butterfield
Great Marlings
Luton
LU2 8DL
UK

Telephone + 44 (0) 1480 402400

Email for data protection/GDPR enquiries companysecretary@tillomed.co.uk

Email for all other purposes PVUK@tillomed.co.uk

When emailing or otherwise contacting the Lead Sponsor You must refer to Patients by their Unique Study Reference Number, year of birth and gender only. This will prevent identification in the event the communication is intercepted by an unauthorised person. The use of year of birth and gender will provide a cross check to the Unique Study Reference Number.

4.1 Adverse events reporting

All adverse events that occur after enrolment of the Patient in the Study through to the final follow-up must be documented in the follow-up form.

4.2 Expedited reporting of serious adverse events

Please note that all serious adverse events require expedited reporting.

(A serious adverse event is any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.)

You must notify the Lead Sponsor about any serious adverse event (SAE) within 24 hours of its appearance, through any available mode of communication e.g. phone or email. You must refer to the Patient by their Unique Study Reference Number and their year of birth and gender only. You must not refer to the Patient's name or any other identifying details.

A detailed report about the SAE will be sent by or on behalf of the Lead Sponsor to the EMA. within 7 working days.

5. Data Protection

Both You (as your employer's representative) and the Sponsors have responsibilities under GDPR. You (or your employer) are data controllers in respect of all the personal data you process about your Patients. The Sponsors are joint data controllers in respect of the personal data You enter in the Registry about You, your Patients and, where applicable, Guardians. The Lead Sponsor is taking responsibility for data protection on behalf of all the Sponsors. Please read the document entitled "Information sharing arrangements between Prescribers and the Lead Sponsor". If You have a question about data protection or the GDPR in relation to the Study, please contact the Lead Sponsor.

5.1 Patient data

Patient data in the Registry (i.e. names on the Patient Information Sheets and ICFs, Unique Study Reference Numbers and the data on baseline data forms and follow-up forms) will be processed by the Lead Sponsor and shared, on a "pseudonymised" basis, with a statistician who will analyse it and provide reports to the EMA.

The pseudonymised data will contain the following information about each Patient:

- Unique Study Reference Number
- Information in the baseline data form and follow-up forms

The statistician will not be able to identify Patients from the data he/she receives.

The information in the statistician's report prepared for the EMA will be aggregated. It will not contain Unique Study Reference Numbers and Patients will not be identifiable.

When You have uploaded the signed combined Patient Information Sheet and ICF to the Registry, please destroy the original or keep it securely in accordance with your employer's, policies and procedures.

To ensure the Patient's data is processed in accordance with the GDPR, when reporting a serious adverse event, or otherwise contacting the Lead Sponsor about an individual Patient, you must refer to the Patient by their Unique Study Reference Number and their year of birth and gender only. You must not refer to the Patient's name or any other identifying details.

If the Lead Sponsor's pharmacovigilance service provider (PV service provider) contacts You about an adverse event and it is determined that the PV service provider should contact the Patient directly, you must obtain, and record, the Patient's (or Guardian's) explicit consent to releasing his/her name and contact details before making them available. If the Guardian is to be contacted, the Guardian's consent must be obtained and recorded to the release of their contact details.

Minors who celebrate their 18th birthdays during the Study period must sign a new consent form before further information about them can be entered in the Registry. Please see **"**Patient Information Sheet and Informed Consent Form" above.

More details about processing of Patients' data, how their privacy will be protected, what will happen to their data if they withdraw from the Study and their rights under GDPR are set out in the Patient Information Sheet.

5.2 Guardian data

The only Guardian data in the Registry will be their names and the fact that they are the person who is legally responsible for the Patient.

Guardian data will not be provided to the statistician.

Please ensure You provide Guardians with a copy of the privacy notice for Guardians before he/she signs the Patient Information Sheet and ICF.

If the Lead Sponsor's pharmacovigilance service provider (PV service provider) contacts You about an adverse event and it is determined that the PV provider should contact the Guardian directly, you must obtain and record the Guardian's consent to releasing his/her name and contact details, and explicit consent to releasing the Patient's name, before making them available.

5.3 Your data

The only data about You in the Registry will be your name, contact details and GMC/GPhC number (or equivalent) and your Prescriber Study Reference ID. You will be identified in data shared with the statistician by your Prescriber's Study Reference ID only. The statistician will not be able to identify You from the data he/she receives. Your Prescriber Study Reference ID will not appear in the reports prepared by the statistician for the EMA.

Your name and contact details may be shared with the Lead Sponsor's pharmacovigilance service provider if they wish to contact You about an adverse event.

Please read the privacy notice for Prescribers.

6. Withdrawal of Patients from Study

If You withdraw a Patient from the Study, the Patient's signed Patient Information Sheet and ICF, baseline and follow up data will remain in the Registry.

If a Patient withdraws from the Study (or is withdrawn by their Guardian), declines to sign a Patient Information Sheet and ICF following their 18th birthday or withdraws his/her consent to processing of their personal data, you must take the following action:

- If possible, have the Patient (or Guardian) sign the withdrawal of notice form and upload it to the Registry.
- If the Patient (or Guardian) cannot/will not sign the withdrawal of notice form, please complete the Prescriber's confirmation of Patient's withdrawal from Study form and upload it to the Registry.
- You must not enter any further information about the Patient in the Registry.

On receipt, the Lead Sponsor will:

- delete the Patient's baseline data and follow-up data from the Registry, but will retain a copy of both the signed Patient Information Sheet and ICF, and notice of withdrawal
- instruct the statistician to remove the Patient's data from the information s/he holds
- if the Lead Sponsor's PV service provider has received the Patient's name and contact details from You, instruct the PV service provider to delete those details so that the remaining information it holds is anonymised.

If the Patient notifies the Lead Sponsor that s/he wishes to withdraw from the Study or withdraws his/her consent to processing of their personal data, the Lead Sponsor will notify You and You must not enter any further information in the Registry.