PASS Information

Title	Cidofovir Exposure Registry Study
Protocol version identifier	Version 1.0
Date of last version of protocol	Not applicable
EU PAS register number	
Active substance	Cidofovir (ATC code: J05AB12; Pharmacotherapeutic Group: antivirals for systemic use)
Medicinal product	Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion
Product reference	Vistide®
Procedure number	UK/H/5536/001/DC
Marketing authorisation holder(s)	Emcure Pharma UK Ltd.
Joint PASS	No
Research question and objectives	The objectives of the study are: ▪ To identify the indications and patient populations for Cidofovir use; ▪ To evaluate patterns and compare rates of adverse events occurring in the on label group with events occurring in the off label group" ▪ To assess patient outcome following treatment in specified indication; (*Based on the data accumulated a comparison of AE type and rate using the "on-label" patient group as comparator would be considered for analysis*)
Country (-ies) of study	United Kingdom, Germany, Belgium and Spain.

Marketing authorization holder(s)

Marketing authorisation holder	**Emcure Pharma UK Ltd.** 3 Howard Road Eaton Socon, St Neots Cambridgeshire PE19 8ET United Kingdom
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APPROVAL PAGE

Project Title: Cidofovir Exposure Registry Study

Protocol ID Number: EMC00001

Version: 1.0

Date:

The protocol has been reviewed and approved by:

_____ _____

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2 List of Abbreviations

AE(s)	Adverse event(s)
AIDS	Acquired Immuno Deficiency Syndrome
Art	Article
ATC	Anatomical Therapeutic Chemical
BE	Belgium
BK Virus	Polyomavirus hominis 1
CD4	Cluster of Differentiation 4
CMS	Concerned Member States
CMV	Cytomegalovirus
DC	Decentralised Procedure
DE	Germany
DIR	Directive
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOCMVD	Extraocular CMV Disease
ES	Spain
EU PAS Register	European Union Post-Authorisation Studies Register
GVP	Good Pharmacovigilance Practices
HAART	Highly Active Anti-Retroviral Therapy
HCP(s)	Healthcare Professional(s)
HIV	Human Immunodeficiency Virus
ISPE	International Society for Pharmacoepidemiology
Ltd.	Limited
MAH	Marketing Authorisation Holder
PASS	Post Authorisation Safety Study
PSUR	Periodic Safety Update Report
REG	Regulation
RMS	Reference Member State

SAE(s)	Serious Adverse Event(s)
SAS	Statistical Analysis System
SPC	Summary of Product Characteristics
UK	United Kingdom

3 Responsible parties

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4 Abstract

4.1 Title

Cidofovir Exposure Registry Study

4.2 Rationale and background

The Applicant Emcure Pharma UK Ltd. received approval on 17th May 2016, for Marketing Cidofovir 75mg/ml concentrate for solution for infusion via Decentralised Procedure (UK/H/5536/001/DC). United Kingdom (UK) is the Reference Member State (RMS); Belgium (BE), Germany (DE) and Spain (ES) are the Concerned Member states (CMS) for the procedure. The application was based on Art 10(1) (generic application) of Directive 2001/83/EC (as amended). "Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion" has been approved for the treatment of Cytomegalovirus (CMV) retinitis in HIV infected subjects. Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion will be referred to as "Cidofovir (Emcure's formulation)" throughout the document as applicable.

Cidofovir is indicated for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. Due to the reduced incidence of CMV retinitis in HIV infected subjects, the availability of alternative treatment options and the restrictions for use imposed by the product information, cidofovir is not expected to be used frequently in this indication. Literature reports indicate that there is off-label use of cidofovir in the treatment of specific viral infections in certain populations of patients.

In view of the concerns relating to the safety of cidofovir, RMS and CMS mandated the Marketing Authorisation Holder (MAH) to implement additional monitoring of Cidofovir (Emcure's formulation) through an exposure Cidofovir Exposure Registry [known as post-authorisation safety study (PASS)]. The obligation has been imposed by the competent authorities in accordance with REG Art 10 and Art 10a and with DIR Art 21a and Art 22a (category 1 of studies in Module V- Risk management systems).

This exposure (safety outcome) Cidofovir Exposure Registry will be a non-interventional, prospective study with an aim to collect data relating to any exposure to Cidofovir (Emcure's formulation) in any of the indications for which the product is used (on or off label) and to characterise the impact of off label use. This study will allow identification of new safety information pertaining to cidofovir usage (on or off label).

In addition to the routine pharmacovigilance plan, a PASS for Cidofovir (Emcure's formulation) will be implemented as a post approval commitment by the MAH in UK, BE, DE and ES.

4.3 Clinicians and pharmacists supplied with Cidofovir (Emcure's formulation) will be informed of the Cidofovir Exposure Registry Study via the cover letter and synopsis which will be circulated with the product. (Annex Synopsis -1.1)Research Question and Objectives

This Cidofovir Exposure Registry is a Post Authorisation Safety Study in accordance to European Union which would fulfill the post marketing commitment. The objectives of the study are:

- To identify the indications and patient populations for Cidofovir (Emcure's formulation) use;
- To evaluate patterns and compare rates of adverse events occurring in the on label group with events

occurring in the off label group

- To assess patient outcome following treatment in specified indication;

(*Based on the data accumulated a comparison of AE type and rate using the "on-label" patient group as comparator would be considered for analysis*)

4.4 Study Design

This is an observational/non-interventional, multi-centre, multi-national, Cidofovir Exposure Registry-based, cohort study with prospective patient enrolment and follow up. The Cidofovir Exposure Registry will spread across UK, Belgium, Germany and Spain. Physicians and hospital pharmacists will be identified in each member state who will enrol potential patients requiring Cidofovir (Emcure's formulation) treatment. -A copy of the synopsis shall be distributed to the HCP along with the product. The baseline and follow-up data will be collected using web-based electronic data capture (EDC) system. As this PASS is a long term safety study, the duration is not specified.

4.5 Population

Patients across UK, Belgium, Germany and Spain who have been prescribed Cidofovir (Emcure's formulation), will be enrolled in the study on a voluntary basis by the HCPs [physicians (Infectious disease specialists, HIV specialists) and hospital pharmacists]. To be eligible for enrolment, the patient should meet the following criteria:

- The patient is exposed to Cidofovir (Emcure's formulation);
- Patient or patient's authorised carer (in event the patient is unable to consent) is willing to provide written informed consent;
- The patient should have reported exposure or outcomes which are verified by a HCP. Any reported exposure or outcome not verified by a HCP, should exclude the patient from the Cidofovir Exposure Registry.

4.6 Variables

Variables include study endpoints [indication (off-label or on-label), renal and other AEs and patient's outcome], patient demographics, comorbid conditions, exposure information, concomitant medications, and laboratory assessments which will be extracted from the electronic Baseline and Follow-up data forms. (Annex 1.2 and Annex 1.3)

4.7 Data sources

Patient information will be electronically recorded at the time of enrolment and during follow- ups using EDC system. These forms will have the data transcribed from medical documents (medical history records, prescriptions, reports of laboratory investigations, etc.).

4.8 Study size

The study size has no upper limit and will depend upon the case reports received following marketing exposure. The minimum anticipated study size will be determined after the statistical evaluation based on the 12 months data collected.

A total of 1610 evaluable patients are required to detect at least 1 uncommon/unknown adverse event with uncommon adverse reaction incidence rate of 0.001 with a statistical power of 80%. Considering 10% dropout rate a total 1770 patients will be enrolled assuming at least one injection for one patient will be received.

4.9 Data analysis

All analysis will be performed using appropriate procedure of SAS® or an equivalent tool. The data will be presented by country and if necessary, according to the age groups. The data analysis for the study endpoints will include the following assessments:

- ✓ The proportion of patients prescribed Cidofovir (Emcure's formulation) as per each indication (on or off label).
- ✓ Proportions of renal AEs to the proportion of other AEs, categorised as on-label or off-label indication, using Z-test, Chi-square test or Fisher's exact test.
- ✓ The incidence of serious adverse events (SAE), the incidence and severity of AEs, and the resolution of the AEs, for each indication.
- ✓ Descriptive statistics of the patient population (patient demographics, clinical characteristics, and comorbid conditions), exposure information, and laboratory assessments.
- ✓ Characterising number of patients "lost to follow up" and "drop outs" during the course of the Cidofovir Exposure Registry further shall be stratified based on on-label or off-label use.

4.10 Milestones

The start date of data collection will be decided after the launch of the product, the subsequent milestones will follow thereafter. Refer ***Section 6 Milestones***, for details.

5 Amendments and Updates

Not applicable.

This is the first version of the protocol.

6 Milestones

Milestone	Planned date	Comment
Registration in the EU PAS register	Q4 2018	-
Start of data collection	March 2019	The data collection will be initiated within 6 months of the protocol being approved
Interim Report	12 months after start of the study	Interim analysis would help in estimating the duration of the study
End of data collection		
Study progress/Annual report	Q4 20	-
Final report of study results	Within 06 months of the end of data Collection	Within 06 months of the end of data collection
Assessment reports	Assessment reports will be prepared and submitted annually	

7 Rationale and background

Regulatory background

Approval via Decentralised Procedure

Emcure Pharma UK Ltd. received approval for the Marketing Authorisation of Cidofovir 75mg/ml concentrate for solution for infusion via Decentralised Procedure (UK/H/5536/001/DC) with UK as the RMS and BE, DE and ES as the CMS. The application was based on Art 10(1) (generic application) of Directive 2001/83/EC (as amended). Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion is indicated in the treatment of CMV retinitis in HIV infected subjects (RMS Day 210 Final Assessment Report).

Post-authorisation commitments

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Cidofovir is indicated for the treatment of CMV retinitis in adults with AIDS and without renal dysfunction. However, due to the reduced incidence of CMV retinitis in HIV infected subjects, the availability of alternative treatment options and the restrictions for use imposed by the SPC, cidofovir is not expected to be used frequently in this indication. Literature reports indicate the off-label use of cidofovir in the treatment of specific viral infections in certain populations of patients.

Further, consultations with UK clinical experts in the field indicate that systemic cidofovir is used off label under specialist supervision by virologists for adenovirus and BK infection, particularly in transplant patients, often as a last resort treatment option in severely ill patients when there is little or no alternative. The morbidity and mortality is very high in these patients, due to a failure of treating such viral infections. The UK clinical experts considered that the availability of cidofovir for these very specific patient populations, who are generally under expert care, is important, even though it was acknowledged that clinical efficacy data are very limited.

In view of the safety concerns due to off-label usage, and considering the importance of availability of cidofovir for the treatment of specific viral infections in certain populations of patients, RMS and CMS mandated the MAH to implement an additional monitoring of Cidofovir (Emcure's formulation) through Cidofovir Exposure Registry surveillance, a PASS. The obligation was imposed by the competent authorities in accordance with REG Art 10 and Art 10a and with DIR Art 21a and Art 22a (category 1 of studies in Module V- Risk management systems).

This Cidofovir Exposure Registry will be a non-interventional, prospective study with an aim to collect data relating to any exposure to Cidofovir (Emcure's formulation) in any of the indications for which the product is used (on or off label) and to characterise the impact of off label use. This will allow identification of new safety information pertaining to Cidofovir usage (on or off label).

In addition to the routine pharmacovigilance plan, a PASS for Cidofovir (Emcure's formulation) will be implemented as a post approval commitment by the MAH in UK, BE, DE and ES.

Clinicians and pharmacists supplied with Cidofovir (Emcure's formulation) will be informed of the Cidofovir Exposure Registry study via the synopsis to encourage enrolment.

CMV retinitis

CMV retinitis is the most common ocular opportunistic infection, representing 90% of the infectious retinitis. About 20-30% of the patients with AIDS develop CMV retinitis. It usually occurs in the late stages of the disease (about 18 months after the declaration of the clinical onset) in patients with a lower limit of CD4 levels of 50/mmc (Chiotan et al, 2014).

Prevalence of CMV

Ford N et al (2013) in a systematic review and meta-analysis reported prevalence of CMV retinitis in low- and middle-income countries. The authors considered 65 studies from 24 countries, mainly in Asia (39 studies, 12 931 patients) and Africa (18 studies, 4325 patients). By region, the highest

prevalence was observed in Asia with a pooled prevalence of 14.0% (11.8%– 16.2%). There was no clear pattern of prevalence over time, which was similar for the period 1993–2002 (11.8%; 95% CI, 8%–15.7%) and 2009–2013 (17.6%; 95% CI, 12.6%–22.7%).

Incidence of CMV

EuroSIDA, a multicentre prospective study conducted during the years 1994-2001, was designed to determine the factors affecting the incidence of CMV end-organ disease (CMVD) in patients with AIDS. Clinical and laboratory data were collected from the charts of 8,556 patients in 63 AIDS clinics in Europe. A total of 707 patients had CMVD at recruitment and at follow-up: 449 with CMV retinitis, 190 with extraocular CMV disease (EOCMVD), and 58 with both. This study describes a decline in the incidence and mortality of CMVR and EOCMVD during the Highly Active Anti-Retroviral Therapy (HAART) era of the HIV epidemic (Yust et al, 2004).

Prior to the introduction of HAART, approximately 30% of individuals infected with HIV developed CMV retinitis at some point during their lifetime. Treatment with HAART suppresses HIV replication, resulting in a drop of HIV load and in immune recovery, as evidenced by a rise in CD4+ T cell counts. As a result, the incidence rates of opportunistic infections, such as CMV retinitis, have declined but they have not dropped to zero (Sugar et al, 2012).

Sugar et al (2012) estimated the incidence of CMV retinitis in a cohort study, in the post- HAART era among 1600 AIDS patients without CMV retinitis at enrolment. They found an incident rate of 0.36/100 person-years, with the highest rate observed among patients with CD4 counts below50 cells/μL.

Cidofovir

Cidofovir 75 mg/mL concentrate for solution for infusion was first approved in Europe more than ten years ago and is currently licensed as an antiviral agent for the treatment of CMV retinitis in HIV infected patients. The reference product "Vistide (Cidofovir) 75mg/ml concentrate for solution for infusion" of Gilead Sciences International Ltd., was first authorised in the EU on 23/04/1997 via the Centralised Procedure (EU/1/97/037/001). On 22 August 2014, the European Commission withdrew the marketing authorisation for Vistide in the European Union at the request of the marketing authorisation holder due to ongoing manufacturing challenges as well as a decreasing incidence of CMV retinitis in adults with AIDS. Currently, HCPs have been using alternative medicinal products and generic medicine containing cidofovir.

Cidofovir is an antiviral nucleotide analogue with significant activity against CMV and other herpes viruses. Cidofovir has a long intracellular half-life which allows for a prolonged interval (2 weeks) between maintenance doses. In contrast, other intravenous treatment options for patients with CMV retinitis (i.e. ganciclovir and foscarnet) must be administered on a daily basis. The efficacy of intravenous cidofovir has been demonstrated in patients with AIDS and previously untreated CMV retinitis in multicentre randomised trials, and in a dose-finding study of cidofovir in patients with AIDS and previously treated relapsing CMV retinitis (Plosker GL & Noble S, 1999).

Cidofovir toxicity

The relatively long dosage interval for cidofovir has been found to have favourable implications in terms of overall treatment costs and patient quality of life, although specific data are very limited. Potentially irreversible nephrotoxicity is the major treatment-limiting adverse event associated with

intravenous cidofovir in patients with AIDS-related CMV retinitis.

Anterior uveitis/iritis has been reported frequently with intravenous cidofovir in post-marketing reports and a small number of patients have developed hypotony (Plosker GL & Noble S, 1999). A long- term follow-up study of patients with AIDS treated with parenteral cidofovir for CMV has reported that although effective for the treatment of CMV retinitis, cidofovir has potential toxicity that typically resolves with discontinuation of therapy. Careful attention to both concomitant therapy and monitoring for toxicity is required (No Authors listed, AIDS. 2000, PMID: 10983644).

Carcinogenic potential of cidofovir

The carcinogenic potential of cidofovir is yet to be established in humans though some evidence has been gathered from animal studies.

A significant increase in incidence of mammary adenocarcinomas with cidofovir has been observed in female rats in two separate studies (26-week IV toxicity study and once weekly subcutaneous injections for 19 consecutive weeks). In both studies tumours were observed within 3 months of dosing. No tumours were observed in cynomolgus monkeys administered IV Cidofovir once weekly for 52 weeks (2.5mg/kg/week).

In humans, the carcinogenic potential with the use of cidofovir has been discussed in some of the publications (with limited information) with no particular mention of mammary carcinomas.

A 3.5-year follow-up study with intralesional cidofovir in paediatric recurrent respiratory papillomatosis (RRP), revealed unpredictable response to cidofovir with no notable adverse outcomes (Chung BJ et al, 2006). Broekema FI & Dikkers FG (2008) conducted literature review on intralesional cidofovir in patients with RRP. Thirty-one articles were identified for this review and a total of 188 RRP patients were described who underwent therapy with intralesional cidofovir. Although the review did not reveal increased risk of laryngeal dysplasia, authors concluded that occurrence of dysplasia during treatment with intralesional cidofovir needs to be evaluated in future trials.

From the above, it may be noted that cidofovir's potential for carcinogenicity remains largely undefined and would require long term follow up studies. Additional follow up after end of cidofovir treatment for each subject is a challenge considering that carcinogenesis does not occur immediately but emerges over a period of time. Therefore, the scope of this Cidofovir Exposure Registry study shall only include collecting and recording the carcinogenic events in patients exposed to cidofovir (Emcure's formulation). MAH shall include a comparison between rates of carcinogenic events between on and off label treatment groups (if sufficient data are gathered).

Off-label use of Cidofovir

Limited information available in the public domain shows that cidofovir has many other potential applications. Examples include intravenous administration of cidofovir for treatment of progressive multifocal leukoencephalopathy and Kaposi's sarcoma, intraocular injection for treatment of CMV retinitis, intralesional injection for treatment of respiratory papillomatosis, topical application for treatment of molluscum contagiosum, anogenital condyloma acuminata, and recurrent genital herpes, and ophthalmic instillation for treatment of viral keratoconjunctivitis [(Safrin S1, Cherrington J, Jaffe HS (1997)].

On-label use of Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion, as defined in the Summary of Product Characteristics, is presented below:

- Cidofovir is indicated for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. It should be used only when other medicinal products are considered unsuitable.

The definition of off-label use of Cidofovir (Emcure's formulation) would include the following circumstances (but not limited to):

- A different indication in term of medical condition than the one described in the authorised product information;
- A different group of patients than the one described in the authorised product information;
- A different route or method of administration than the one described in the authorised product information;
- A different posology than the one described in the authorised product information.

Clinicians and pharmacists supplied with Cidofovir (Emcure's formulation) will be informed of the Cidofovir Exposure Registry Study via the cover letter and synopsis which will be circulated with the product. **(Annex Synopsis -1.1)** Clinicians and pharmacists shall be periodically reminded regarding the Cidofovir Exposure Registry Study via methods described in section 9.1.1 Methodology.

8 Research question and objectives

Cidofovir Exposure Registry studies on the use of drugs (both off and on) are essential to evaluate the intended and adverse effects of prescription medications as they are used in clinical practice across populations under different health care systems. The description of users of Cidofovir (Emcure's formulation) according to their clinical indication for use will allow for the evaluation of potential off-label use.

The objectives of the study are:

- To identify the indications and patient populations for Cidofovir (Emcure's formulation) use;
- To evaluate patterns and compare rates of adverse events occurring in the on label group with events occurring in the off label group
- To assess patient outcome following treatment in specified indication

(*Based on the data accumulated a comparison of AE type and rate using the "on-label" patient group as comparator would be considered for analysis*)

9 Research methods

Observational research methodology will be applied to accomplish the objectives listed above.

9.1 Study Design

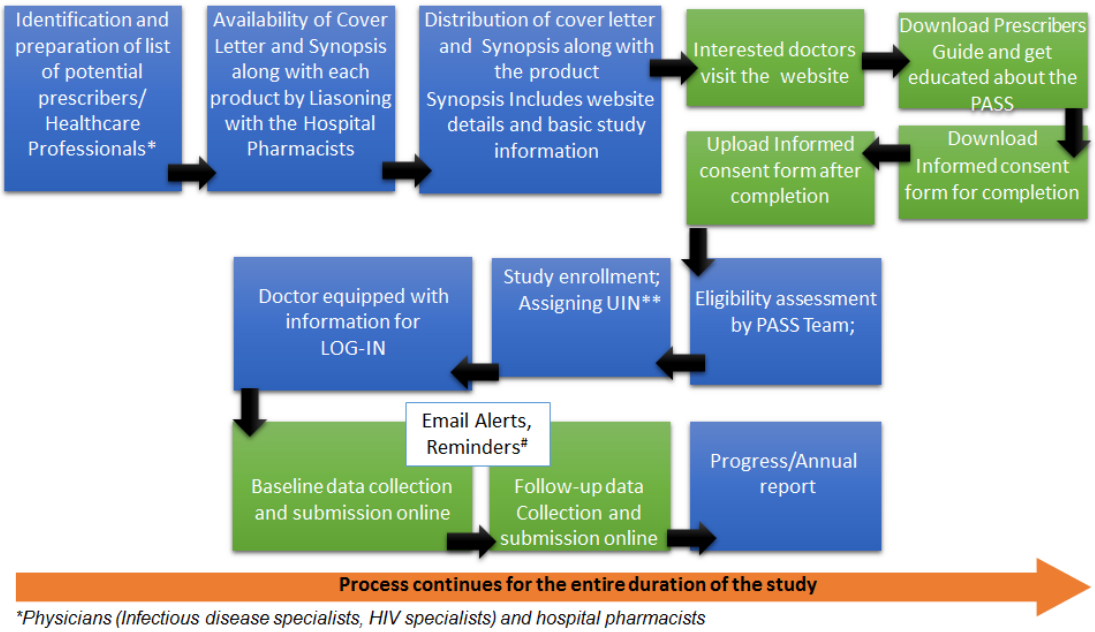
This is an observational/non-interventional, multi-centre, multi-national, Cidofovir Exposure Registry-based, cohort study with prospective patient enrolment and follow up. There is no specific duration for the study. Long term safety data will be collected.

The endpoints of this study are:

- Proportion of patient population per indication, using Cidofovir (Emcure's formulation);

- Frequency and severity of renal events in comparison to all AEs;
- Frequency of patients experiencing AEs per indication;
- Proportion of patients as per the treatment outcome (e.g. treatment discontinuation due to AE/SAE, resolution of underlying illness, completion of treatment regimen, death of the patient, lost to follow-up).
- Comparison of AE type and rate using the "on-label" patient group as comparator.

Figure 1: Overall Study Flow



**Physicians (Infectious disease specialists, HIV specialists) and hospital pharmacists*
***UIN: Unique Identification number*
 # In case, follow-up information is not received within 15 days after first dose, an Auto email would be sent to the prescriber requesting further information Reminders in form of mailers along with synopsis and cover letter would be sent again to potential prescribers from a particular potential Centre in the event of non-enrolment of relevant patients in the Cidofovir Exposure Registry every 15 days

9.1.1 Methodology

Identification of Healthcare Professionals

Physicians (Infectious disease specialists, HIV specialists) and hospital pharmacists will be identified in each member state who will enrol potential patients requiring Cidofovir (Emcure's formulation) treatment. These HCPs or their designee will be responsible for capturing patients' data pertaining to various treatment modalities (both off and on-label) including the occurrence of any untoward events during the course of the study.

The synopsis will be used to encourage HCPs to enrol patients in this Cidofovir Exposure Registry study and also to make them aware of the drug and its usage in various subsets of patients for approved and off label use. This will facilitate the monitoring of safety and notification of SAEs.

The MAH will ensure that Healthcare Professionals who prescribe Cidofovir (Emcure's formulation) will have access to the Synopsis. This synopsis will be provided to the distributors along with each supply of the product and on the Cidofovir Exposure Registry Study dedicated website.

Protocol for improving low enrolments and poor follow-up rates

- From the database of the enrolled patient based on the first Cidofovir (Emcure's formulation) date, a fortnightly notification in form of reminder mailers may be sent to the HCPs who have enrolled patients in the Cidofovir Exposure Registry Study, if follow-up information is not received.
- The identified centers with potential prescribers and their participation shall be monitored/tracked to ensure maximum participation. Since the potential list of prescribers is already identified and patient enrolments would be tracked for the Registry, the non-participating centres would be shortlisted and reminder mailers would be send every 15 days.
- HCPs would be informed that they could enroll patients prescribed Cidofovir (Emcure's formulation) for off-label indication too. Only in Germany no follow-up information would be sought for patients prescribed Cidofovir (Emcure's formulation) for an off-label use.

Prescriber's Guide

Should the physician require any further information in addition to the synopsis, then they can access the prescribers guide on the website. **(Annex 1.2)**

Eligibility assessment, Patient enrolment, Assigning UIN

Patients across UK, Belgium, Germany and Spain prescribed Cidofovir (Emcure's formulation) will be enrolled in the study on a voluntary basis by the prescribers. Patients who sign the informed consent document **(Annex 1.)** and meet the eligibility criteria will be enrolled in the study. This needs to be submitted via the website. Each prescriber will then be allotted with a user name and password corresponding to that patient. This will allow for the prescriber to login using the website in order to create a patient profile on the EDC system by filling the baseline details of the patient in the electronic forms. The hospital /medical records will serve as the source documents for capturing data in the EDC.

Data recording

Baseline data will be recorded during recruitment and follow-up data will be recorded 'at subsequent follow-ups". Refer Annex 1.4 for Baseline Data Form and Annex 1.5 Follow-up Form.

Patient Information

The baseline data that will be collected at the time of enrolment are listed below:

- Patient demographics (age and gender);
- Medical history;
- Treatment details (which include indication and treatment regimen);

- Exposure information (dose, route and frequency of administration, duration of treatment);
- Results of laboratory investigations [haematology, biochemistry (including urea, creatinine, phosphate, uric acid, bicarbonate), Urine analysis (including glycosuria), Serology, etc.].
- Concomitant medications

Follow-up Information

At the follow-up visit* following information will be collected:

- Exposure information (dose, route and frequency of administration, duration of treatment);
- Results of laboratory investigations [haematology, biochemistry (including urea, creatinine, phosphate, uric acid, bicarbonate), Urine analysis (including glycosuria), Serology, etc.].
- Concomitant medications;
- Occurrence of all AEs including carcinogenic events, targeted events of interest (Nephrotoxicity including Fanconi syndrome and renal failure), and serious adverse events (SAEs).

- Patient's outcome: At end of the treatment, the following data would be submitted:
  - ✓ Any AE, with special reference to nephrotoxicity including Fanconi syndrome and renal failure.
  - ✓ Outcome of AE: resolved, resolved with sequelae, not resolved.
  - ✓ Details of treatment: duration of use, total dose received, frequency of administration
  - ✓ Outcome of treatment e.g.: treatment discontinued due to AE, underlying illness resolved, treatment regimen complete, death of patient, lost to follow-up.

* For the implementation of the Cidofovir Exposure Registry in Germany, as per the German Medicines Act it will not be possible to follow up patients treated off-label as this would be regarded as a violation of the definition of a non-interventional trial as per the German Medicines Act. Therefore to comply with German law:

- For patients treated off-label, only demographic data, type of off-label use (e.g. regarding dosage, administration route or indication, contraindicated conditions, use in unapproved patient population) and indication should be recorded. No further data collection should take place thereafter. No further data should be collected on patients treated off-label within the registry.
- For patients treated in-label data collection should however follow the multinational protocol. Therefore, the Cidofovir Exposure Registry should collect baseline data and follow-up data only for patients treated in line with the approved label for approved indication and for patients without any contraindication in line with the approved SmPC."
- Follow up data should be reported at any point following patient exposure and more than one follow up form can be submitted per patient.
- A minimum data should be submitted once, following the end of the treatment regimen.

Table 1: Schedule of events

Study Visits	**Baseline Visit**	**Follow- up Visit***
Parameters		
Informed consent and eligibility	**X**	
Inclusion/ Exclusion Criteria	**X**	
Generating unique patient identification number	**X**	
Demography data	**X**	
Cidofovir treatment details**	**X**	**X**
Relevant medical history	**X**	
Concomitant medication	**X**	**X**
Laboratory Investigations	**X**	**X**
Patient's outcome		**X**

***Follow–up visit(s) can be any time after the baseline visit.** Follow up data should be reported at any point following patient exposure and more than one follow up form can be submitted per patient, however as a

minimum data should be submitted once following the end of the treatment regimen. The follow-up detail has also been included in the Fig 1: Flow of events in Section 9.1 Study Design

****Includes recording of Indication, dose, frequency, route of administration and duration of treatment**

9.2 Setting

9.2.1 Study Centres

The study centres will be spread across UK, Belgium, Germany and Spain. For UK,BE, DE and ES the approval was granted on 10th June 2016,1st August 2016, 11th October 2016 and 8th March 2017 respectively

9.2.2 Eligibility Criteria

The study will be carried out at HIV and infectious disease centres identified by Emcure Pharma UK Ltd. Hospital pharmacists in these centres will be supplied with Cidofovir (Emcure's formulation). The pharmacists will be made aware of the Cidofovir Exposure Registry study and will be informed to encourage the prescribers for patient enrolment through the Cover Letter and Synopsis. The prescribers will assess the eligibility and enroll patients who meet the following criteria:

Inclusion Criteria

- Patients exposed to Cidofovir (Emcure's formulation)
- Patient or patient's authorised carer (in event the patient is unable to consent) willing to provide written informed consent.

Exclusion Criteria

- Patients who have reported exposure or outcomes which have not been verified by a HCP.

9.3 Variables

Variables include study endpoints [indication (off-label or on-label), renal and other AEs and patient's outcome], patient demographics, comorbid conditions, exposure information, concomitant medications, and laboratory assessments which will be extracted from the electronic Baseline and Follow-up data forms.

Off-label use will be evaluated by use of Cidofovir (Emcure's formulation) in different indications, patient population, route of administration and posology, other than approved in the product information.

Exposure to cidofovir use will be measured by determining the dose, duration, frequency and route of administration in any indication (on label/off label).

9.4 Data sources

Patient information will be electronically recorded at the time of enrolment and during follow- ups using EDC system. These forms will capture the data transcribed from medical documents (medical history records, prescriptions, reports of laboratory investigations, bed-side notes, etc.).

The forms (Baseline Data Form and Follow-up Data Form) are available as annexures (Annex 1.4 and 1.5 List of stand-alone documents).

9.5 Study size

Patient treated days (PTD) in the past years, has been attempted in order to evaluate the feasibility of the study, and latest available data has been considered.

PTD = Number of packs sold x pack size/ Number of units taken by patient daily

PTD= 43332 X 1/0.33 = 1,31,309

Total unit sales for EU and US= 43,332. The total unit sales of US and EU has been considered for calculation. The sales in the USA is higher than in EU.
Pack size=1
As per WHOCC-ATC/DDD index[2] the Defined Daily Dose (DDD) for cidofovir is 25mg.
Based on this recommendation, it has been assumed that number of unit taken daily by the patient for 75 mg/ml is 0.33 unit respectively.

In order to obtain a statistically meaningful safety data for Cidofovir registry study, Emcure Pharma considered the cumulative adverse event cases data received as well as the global sales of cidofovir during the period June 2016 to June 2018. For the purpose of comprehensive data calculation, Emcure has included the spontaneous cases as well as cases derived from scientific literatures from worldwide.

Until June 2018 a total of 23 cases were received by Emcure cumulatively out of which 8 were received from Europe and 15 were received from USA. Only two cases were received spontaneously to company and remaining were derived from scientific literature. Except for one case, in all remaining cases Cidofovir 75mg/ml concentrate for solution for Infusion was used as off label either for an off-label indication (adenovirus infection, HPV and along with Acyclovir in the treatment of Herpes Simplex Virus-1) or unapproved route of

administration (intralesional, topical). In total, 26[1] adverse[2] events (preferred terms) were reported in these 23 cases.

Period	Total unit sales	Cases reported
From June 2016-June 2018	43,332	23

Total number of unit sales reported across all the above marketed countries were found to be 43332. The cumulative patient exposure to the Cidofovir 75mg/ml concentrate for solution for
Infusion in terms of patient treatment days is estimated to be approximately 1, 31,309.

Subsequently, the obtained incidence rate of adverse event was found to be 0.0006 (26/43,332). A total of 2682 evaluable patients are required to detect at least 1 reportable event with statistical power of 80%. Considering indication [treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction] and long duration of treatment i.e. induction (5 mg/kg administered once weekly for two consecutive weeks) and maintenance (5 mg/kg administered once every two weeks) treatment as long as possible based on an acceptable benefit/risk balance of cidofovir therapy, as judged by the physician experienced in the management of HIV infection, with an additional 10% dropout rate, a total sample size of 2951 patients will be enrolled in order to obtain a statistically meaningful data.

The formulae used to arrive the calculations

$$\sum_{x=0}^{a-1} \frac{(N\lambda)^x e^{-N\lambda}}{x!} = \beta$$

Considering a =1,

$$N = \frac{-\log \beta}{\lambda}$$

λ = Expected incidence rate of adverse reactions.

[1] Adverse events

PT Name	Number
Renal failure	5
Renal impairment	3
Transplant dysfunction	1
Pulmonary function test decreased	1
Condition aggravated	4
Hepatic function abnormal	1
Drug dispensing error	1
Haematuria	1
Abdominal pain lower	1
Fluid overload	1
Nephropathy toxic	2
Gastrointestinal haemorrhage	1
Gastrointestinal disorder	2
Cytomegalovirus infection	1
Abdominal discomfort	1

[2] Reportable events includes all adverse events/reactions of medicinal product

a = The number of occurrence of a particular event.
N = Required sample size which need to be estimated.
1-ß = Statistical power

Considering total adverse events as		26
Total number of units sale from the product launch		43332
λ	Expected incidence rate of ADR	**0.0006**

Power	**[-log(β)]**	**N**
50%	0.693147	1155
60%	0.916291	1527
70%	1.203973	2007
80%	1.609438	2682
90%	2.302585	3838
95%	2.995732	4993
	Including 10% dropout rate	2951

Duration of the study:
Based on the limited available data of adverse events versus sales of Emcure's Cidofovir injection, it is challenging to estimate the exact duration of the study based on number of patients.
Considering the low incidence of the CMV retinitis, majority of off label reports received so far and limited adverse event data, Emcure proposes to have the registry conducted for a longer duration. Currently, based on the statistical calculation of number of patients needed, estimating exact duration of study would not be appropriate and justifiable. It would be an organized data collection and adequate efforts would be taken to encourage HCPs to enroll patients and report safety related information as soon as the Cidofovir Exposure Registry starts. Instead of defining the duration of the Cidofovir Exposure Registry in the beginning, Emcure proposes that the received data is evaluated for number of patients getting enrolled and the type of data being received at the end of two years after the start of study. After completion of two years of study, with the data received, the further duration of the study can be estimated and shall be proposed to authority to obtain meaningful data for analysis.

9.6 Data management

9.6.1 Data collection

Data will be routinely collected from patients who will be prescribed Cidofovir (Emcure's formulation) by the prescriber. A web-based EDC system will be used in this study for prescriber. Electronic forms and company sponsored website will be set up to collect this information and allow submission of electronic reporting. Two electronic reporting forms will be used – one to

collect the baseline data, and the other to capture the follow-up data linked to each patient.

If the prescriber would like to enrol a patient for the study they must visit www.cidofovir.eu. On the website they must refer to the dedicated page which will allow them to download and upload the respective patient enrolment forms.

Upon upload, each prescriber will be allotted with a patient specific user name and password at the time their profile is created on to this EDC system which they will receive by email. This number would facilitate the prescriber to link between the 'Baseline data form' and the 'Follow-up data form' concerning the same patient. Data collected should only be that which is part of the best practices followed by the physician, as this is an observational study.

Data will be collected at

- enrolment and
- when the patient is being followed up.
- until patient no-longer needs Cidofovir
- until treatment is discontinued permanently for any reason
- until study is no longer required.

All necessary information will be gathered from patient medical records and entered into the EDC system. The Cidofovir Exposure Registry representative will periodically contact the HCP to ascertain any AEs and outcome of treatment and AEs.

9.6.2 Data Handling

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. Patients' data will be entered into EDC system by the prescribers or their designee. Edit and logical checks will be programmed into the EDC system to ensure high-quality data.

Data from the website shall be automatically captured on our company secure server. The information on the database would be encrypted and only authorised personnel will be allowed access by way of username and password. We will also be enforcing IP restrictions so that access is controlled within the company.

9.7 Data Analysis

- The data analysis for the study endpoints will include the following assessments:
  - ✓ The proportion of patients prescribed Cidofovir (Emcure's formulation) will be evaluated for each indication (on or off label). Both relative frequencies and ratio frequencies will be calculated.
  - ✓ Proportions of renal AEs to the proportion of other AEs will be compared using a Z-test to mark the frequency of renal events in comparison to all AEs. A Chi-square test (or Fisher's exact test, if the data is very small) will be used to compare the proportion of renal AEs versus other AEs, further categorised as per the prescribed indication (on or off label).

- ✓ The incidence of serious adverse events (SAE), the incidence and severity of AEs, and the resolution of the AEs, for each indication will be assessed.
- ✓ Analyses, including descriptive statistics of the patient population (patient demographics, clinical characteristics, and comorbid conditions), exposure information, and laboratory assessments will be performed.
- ✓ The study will also characterise number of patients "lost to follow up" and "drop outs" during the course of the Cidofovir Exposure Registry further shall be stratified based on .on-label or off-label use as will be identified from the information in the Baseline data form.

- Survival analysis techniques (Kaplan-Meier graphs and life tables) will be used for time to event outcomes such as duration of treatment for on label and off label indications. If there is enough data, the duration of treatments will be compared.
- The data will also be presented by country and if necessary, according to the age groups.
- Categorical variables will be described using frequencies and percentages, while continuous variables will be summarised using means, standard deviations, medians, and inter-quartile ranges.
- As data accrues, individual analysis plans will be developed to perform secondary analyses to compare the usage of study drug for on-label indications and off-label indications.
- All analysis will be performed using appropriate procedure of SAS® or an equivalent tool.

9.8 Quality Control

Prescriber will be responsible for ensuring the data quality and integrity, including archiving of medical documents (medical history records, prescriptions, reports of laboratory investigations, etc.).

MAH will ensure data collected and processed during the study will be as per the Data Protection Directive of European regulations (Directive 95/46/EC).

9.9 Limitations of research methods

The design of the Cidofovir Exposure Registry study mainly allows capturing of information on Cidofovir (Emcure's formulation) use and assesses the extent to which Cidofovir (Emcure's formulation) is prescribed outside of its authorised indication, i.e. CMV retinitis in HIV infected subjects.

The study will be able to estimate the proportion of off-label use and the pattern of Cidofovir use in the general population including the paediatric population.

The main limitations of this planned research are as follows:

- Treatment with HAART suppresses HIV replication, resulting in a drop of HIV load and in immune recovery. As a result, the incidence rates of opportunistic infections, such as CMV retinitis, have declined over the period but they have not dropped to zero. Hence possibility of finding these patients, may be difficult thereby making the recruitment a challenge.
- Non-clinical carcinogenicity has been scarcely reported. No comprehensive evidence in humans has been reported. A long term follow-up post exposure study would probably provide a comprehensive outcome in this regard. In this study, the carcinogenic events will be recorded, however would not be followed up for treatment outcome as these events take a long time to develop.
- Germany is one of the CMS of this procedure (UK/H/5536/001/DC). The national legislation in Germany does not allow capturing of any off-label usage of Cidofovir. Therefore the information gathered in this region would matter strictly for the approved indication alone.
- There might be missing data due to recall bias of the patient or missing data on the clinical records, which might impact the results.

9.10 Other aspects

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. The ENCePP Checklist for Study Protocols is available as Annex 2. The study will be registered in the ENCePP electronic register of post-authorisation studies (EU PAS register) as detailed in the module VIII of the Guideline on Good Pharmacovigilance Practices (GVP).

10 Protection of human subjects

Institutional Review Board (IRB) approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations. In addition, the legal and IRB requirements for accessing and using de-identified, individual, patient–level data will be followed. Approval will be obtained from the IRB.

10.1 Informed Consent

The study-specific Informed Consent Document (Annex 1.3 Informed Consent Document), written in the local layman language (that is understandable to the patient) will be presented to the patient. The patient will be given ample time to read and understand and sign the informed consent document prior to study participation. No study-specific procedures will be performed prior to written consent from the study patient.

10.2 Participant Confidentiality

Data protection and privacy regulations will be observed while collecting, processing, and storing patient's data during the study. The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E and with the 2013 Guideline on GVP module VIII on PASS. All data collected in the study will be de-identified with no breach of confidentiality with regards to personal identifiers or health information.

10.3 Compensation

As this is a non-interventional study using de-identified information from health care practice setting, no compensation will be provided to patients.

Physicians may be paid nominal incentives as a compensation for their time incurred in filling and completing the electronic data forms on EDC system.

11 Management and reporting of adverse events/ adverse reactions

All adverse events that occur after recruitment of the patient in the study through the final follow-up will be documented as per current guidelines from the International Society for Pharmacoepidemiology and the EMA Guideline on GVP Module VI (Management and reporting of adverse reactions to medicinal products). In case of an adverse event, the prescriber/designee will initiate appropriate measures.

Physicians should report adverse events encountered at any point in the study. Causality will be based on the Physician's assessment of the event as related or not related.

The study will include expedited reporting of serious adverse event. A serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life - threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The selected prescribing physician/designee will notify the Sponsor about any serious adverse event within 24 hours after its appearance, through any available mode of communication e.g. phone, fax etc. A detailed report on the serious adverse event will be sent to RMS and all CMS within 7 working days.

All adverse events will be recorded and communicated to the Sponsor at the following email address: safety.eu@emcure.co.in. The Sponsor will collect and provide the adverse event information to the regulatory authorities as specified in Section 12.

It is to be noted that the carcinogenic events will also be recorded on the follow-up form. Requirement for follow-up would be defined on a case by case basis, and may not necessarily be undertaken until outcome. As these events take a long time to develop the number of events that may occur during the study may be too few and performing a statistical test that will provide a meaningful analysis/result would be difficult. According to the available evidence only one case has been reported in which the patient developed squamous cell carcinoma which could largely be associated with the preexisting chronic papilloma virus infection. However, if cases of carcinogenic events are received an analysis of the case report would be done and compared with relevant literature evidence. Any new safety related information about Cidofovir (Emcure's formulation) if available during the study will be communicated in a timely manner. This information will be included in the patient's Informed Consent Document and will be discussed with the patient during the study as needed. The prescribers involved in the study will also be notified of new safety information.

Intensity of Adverse Events: Intensity of adverse events will be assessed as per the following classification:

- Mild: Events are those that are easily tolerated by the subject
- Moderate: Events that cause sufficient discomfort or interfere with the daily activities of the patient and/ or require a simple dose of medication, e.g., analgesics or antiemetics.
- Severe: Events that prevent the patient's daily routine activities and require complex medication or hospitalisation.

12 Plans for disseminating and communicating study results

As per Module VIII (Post-authorisation safety studies) of the 2013 GVP guideline, this Cidofovir Exposure Registry will be included in the EU PAS register (Website: http://www.encepp.eu/encepp studies/indexRegister.shtml). The assessment report will be prepared annually in accordance with the EMA *Guideline on GVP Module VIII* and submitted to the RMS and CMS for their review. Subsequently –cumulative summary of data both for the year gone by and the following year will be provided for authorities review.

The study status and results will also be included in regulatory communications such as the Risk Management Plan and Periodic Benefit-Risk Evaluation Report (PBRER). The final study report will be submitted within 12 months of the end of data collection.

Dissemination and communication of findings from this Cidofovir Exposure Registry will be in accordance with the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* and the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII*. The study results may be published following the guidelines of the International Committee of Medical Journal Editors (ICMJE).

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14 Annexures

Annex 1: List of stand-alone documents

Annex 1.1 Cover Letter and Synopsis

Annex 1.2 Prescriber's Guide

Annex 1.3 Informed Consent Document

Annex 1.4 Baseline Data Form

Annex 1.5 Follow-up Form

Annex 2: ENCePP checklist for study protocol

Annex 3: Additional information

None