Public Assessment Report

Decentralised Procedure

Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion

(Cidofovir)

Procedure No: UK/H/5536/001/DC

UK Licence No: PL 42117/0001

Emcure Pharma UK Limited
LAY SUMMARY

Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion (Cidofovir)

This is a summary of the Public Assessment Report (PAR) for Cidofovir Emcure Pharma Concentrate for Solution for Infusion (PL 42117/0001; UK/H/5536/001/DC). It explains how Cidofovir Emcure Pharma Concentrate for Solution for Infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Cidofovir Emcure Pharma Concentrate for Solution for Infusion.

For practical information about using Cidofovir Emcure Pharma Concentrate for Solution for Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Cidofovir’ or ‘Cidofovir Concentrate for Solution for Infusion’ in this report.

What is Cidofovir and what is it used for?
Cidofovir is a ‘generic’ medicine. This means that Cidofovir is similar to a ‘reference medicine ‘already authorised in the EU called Vistide 75 mg/ml Concentrate for Solution for Infusion may be referred to as ‘Vistide’ in this report.

Cidofovir is used to treat an eye infection called CMV retinitis in patients with AIDS (Acquired Immunodeficiency Syndrome). Cidofovir will not cure CMV retinitis but may improve the condition by delaying progression of the disease.

The safety and efficacy of cidofovir has not been demonstrated in diseases other than CMV retinitis in patients with AIDS.

What is CMV retinitis?
CMV retinitis is an eye infection caused by a virus named cytomegalovirus (CMV). CMV attacks the retina of the eye and may cause loss of vision, and eventually lead to blindness. Patients with AIDS are at high risk of developing CMV retinitis or other forms of CMV disease such as colitis (an inflammatory bowel disease). Treatment for CMV retinitis is necessary to reduce the potential for blindness.

How does Cidofovir work?
Cidofovir Concentrate for Solution for Infusion contains the active substance cidofovir. Cidofovir is an antiviral medicine which blocks the replication of CMV by interfering with viral DNA production.

How is Cidofovir Concentrate for Solution for Infusion used?
Cidofovir is available as a concentrate for solution for Infusion. Cidofovir is, after dilution, administered by intravenous infusion (a drip into a vein) in a hospital setting by a doctor or nurse with appropriate experience in treating people with AIDS.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Cidofovir can only be obtained on prescription.
What benefits of Cidofovir have been shown in studies?
No additional clinical studies were needed as Cidofovir is a generic medicine that is an aqueous solution that is given by injection and contains the same active substance as the reference medicine, Vistide (Gilead Sciences International Limited, UK).

What are the possible side effects of Cidofovir?
Since Cidofovir is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

The most common side effect observed with Cidofovir is damage to the kidneys.

Very common side effects:
(These can affect more than 1 user in 10)
low white blood cell counts, headache, nausea, vomiting, protein in the urine, increase in blood creatinine (a measure of kidney function), hair loss, rash, weakness/fatigue and fever.

For the full list of all side effects reported with Cidofovir, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Cidofovir.

Why is Cidofovir approved?
It was concluded that, in accordance with EU requirements, Cidofovir has been shown to have comparable quality and is considered to be bioequivalent to Vistide (Gilead Sciences International Limited, UK). Therefore, the view was that, as for Vistide (Gilead Sciences International Limited, UK), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Cidofovir?
A Risk Management Plan has been developed to ensure that Cidofovir is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Cidofovir, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provision in the Cidofovir product information, the RMP includes educational activities/training and materials to encourage healthcare professionals to enroll their patients in a Cidofovir observational Registry Program to monitor and facilitate the safe and effect use of Cidofovir.

Other information about Cidofovir.
Belgium, Germany, Spain and the UK agreed to grant a Marketing Authorisation for Cidofovir Emcure Pharma Concentrate for Solution for Infusion on 17 May 2016. A Marketing Authorisation was granted in the UK to Emcure Pharma UK Limited on 10 June 2016.

The full PAR approved for Cidofovir follows this summary.

For more information about treatment with Cidofovir, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I  Introduction  Page 5
II  Quality aspects  Page 6
III Non-clinical aspects  Page 8
IV  Clinical aspects  Page 9
V  User consultation  Page 11
VI Overall conclusion, benefit/risk assessment and recommendation  Page 11
Annex 1- Table of content of the PAR update for MRP and DCP  Page 15
Scientific discussion

I.  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Cidofovir Emcure Pharma 75 mg/ml Concentrate for Solution for Infusion (PL 42117/0001; UK/H/5536/001/DC) could be approved. The product is a prescription-only medicine (POM) and 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 application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Germany and Spain as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Vistide 75 mg/ml concentrate for solution for infusion (Gilead Sciences International Limited, UK), which was first authorised in the EU via the Centralised Procedure on 23 April 1997.

On 22 August 2014, the European Commission withdrew the Marketing Authorisation for Vistide (Cidofovir) in the European Union (EU) at the request of the marketing authorisation holder, Gilead Sciences International Limited. Due to manufacturing problems the product had been in short supply in the EU since February 2013. During the shortage, alternative medicinal products and generic versions of Cidofovir have been used. Due to ongoing manufacturing challenges as well as a decreasing incidence of CMV retinitis in adults with AIDS, Gilead Sciences International Limited decided to request the withdrawal of the Marketing Authorisation for Vistide.

The active ingredient, Cidofovir, is an acyclic nucleoside analogue known to target DNA polymerase and prevent viral transcription and replication. Cidofovir has activity in vitro and in vivo against cytomegalovirus and other members of the herpesvirus family, as well as certain other DNA viruses. After uptake into cells it is converted enzymatically to Cidofovir diphosphate, a structural analogue of deoxycytidine triphosphate, which selectively inhibits viral DNA polymerases relative to host cell polymerases. Clinical studies of intravenous Cidofovir in cytomegalovirus retinitis in patients with AIDS are claimed to show delay of retinitis progression with maintenance doses given once every 2 weeks.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substance as the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 17 May 2016. After a subsequent national phase, a licence was granted in the UK to Emcure Pharma UK Limited on 10 June 2016.

II. QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear and colourless, sterile solution. Each ml of solution contains 75 mg of anhydrous Cidofovir. Each vial contains 375 mg/5ml anhydrous Cidofovir as the active substance.

The product also contains sodium hydroxide (for pH – adjustment), hydrochloric acid (for pH – adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in 5 ml clear glass single-use vials, each with a 5 ml nominal fill volume. The container/closure components include: Type I clear highly resistant borosilicate glass vials, each with a dark grey bromobutyl rubber stopper, and aluminium seal with a flip off plastic tab. Each pack contains one 5 ml vial.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCE

Cidofovir dihydrate

INN: Cidofovir

Chemical name: \([(1S)-2-(4-Amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl) ethoxy] methyl] phosphonic acid dihydrate;
\[(S)-1-[3-hydroxy-2-(phosphonylmethoxy) propyl] cytosine dihydrate.\]

Molecular formula: \(C_8H_{14}N_3O_6P.2H_2O\)

Structure:

\[
\text{\begin{center}
\includegraphics[width=3cm]{structure.png}
\end{center}}
\]

Mr: 315.22

Appearance: White to off-white crystalline powder.

Solubility: Sparingly soluble in water, soluble in 0.1M sodium hydroxide and practically insoluble in methanol and in ethanol.

Stereoisomerism: The cidofovir molecule contains one chiral carbon atom thus exhibits optical isomerism.
Polymorphism

Polymorphism is not reported in the literature for cidofovir.

Cidofovir is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to produce a safe, efficacious, stable concentrate for solution for infusion that was equivalent to the reference product Vistide (Cidofovir 75 mg/ml Concentrate for Solution for Infusion; Gilead Sciences International Limited, UK). Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been approved for the undiluted product, with the special storage conditions “Do not store above 25°C. Do not refrigerate or freeze.” has been accepted.

From a microbiological point of view, the product must be used immediately. Partially used vials should be discarded.
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2-8°C when dilution is performed under controlled and validated aseptic conditions. Storage beyond 24 hours or freezing is not recommended. Refrigerated solutions should be allowed to warm to room temperature prior to use.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support this type of application for a parenteral product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Cidofovir 75 mg/ml Concentrate for Solution for Infusion.

**II.5 Summary of Product Characteristics (SmPC), package leaflet and labelling**
The SmPC, package leaflet and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and package leaflet is available on the MHRA website. The current labelling is presented below:

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of cidofovir are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**III.2 Pharmacology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

**III.3 Pharmacokinetics**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

**III.4 Toxicology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

**III.5 Ecotoxicity/Environmental Risk Assessment (ERA)**
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.
III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

It is recommended that a Marketing Authorisation is granted for Cidofovir 75 mg/ml Concentrate for Solution for Infusion, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of Cidofovir is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

All the relevant clinical information provided is literature based. The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

No new safety data have been submitted and none are required for this type of application.

IV.2 Pharmacokinetics
The pharmacokinetic properties of Cidofovir are well known and are adequately described in the applicant’s clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of Cidofovir are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of cidofovir is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
The safety profile of cidofovir is well known. No new safety data have been submitted with this application for the proposed indication and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cidofovir 75 mg/ml Concentrate for Solution for Infusion

A summary of safety concerns is listed in the table below:
Routine pharmacovigilance activities are proposed to monitor the majority of safety concerns described in the Risk Management Plan. For the safety concern of “Off label use” a protocol synopsis has been provided for a Cidofovir product registry which has been included as an additional pharmacovigilance measure. The registry is a Category I study and the product is considered an Additional Monitoring product. The aim of the registry will be to collect data relating to any exposure to cidofovir in any of the indications for which the product is used (on or off label) and to characterise the impact of off label use. The full protocol was submitted in August 2016 and is currently under assessment.

Additional risk minimisation material in the form of material to encourage healthcare professionals to enrol their patients in the registry has also been included.

In addition to routine risk minimisation activities, the applicant has agreed to the following additional risk minimisation measures:

- Educational material aimed at encouraging healthcare professionals to enroll patients in the prospective observational Registry Program to monitor the safety of use of cidofovir. This material will be targeted at pharmacists who will provide the material to prescribers.
  The educational material contains:
  - Summary of Product Characteristics
  - Information for healthcare professionals

**IV.7 Discussion of the clinical aspects**

It is recommended that a Marketing Authorisation is granted for Cidofovir 75 mg/ml Concentrate for Solution for Infusion.
V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Cidofovir 75 mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

Efficacy
No new clinical data were submitted and none were required for this type of application. No bioequivalence studies were submitted or required for this application for a parenteral product.

SAFETY
The safety profile of Cidofovir is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical safety concerns have been identified. Cidofovir is a well-known active substance. Extensive clinical experience with cidofovir in the proposed indication is considered to have demonstrated the therapeutic value of the compound.

Literature reports indicate that there is off-label use of Cidofovir in the treatment of specific viral infections in certain populations of patients. 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 of failure to treat such viral infections in these patients are very high. 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. At the same time, due to the high acute mortality, long term safety concerns, specifically the carcinogenicity observed in non-clinical studies, may be less of a concern in these populations.

In view of the concerns relating to the safety of Cidofovir, the company has agreed to implement additional pharmacovigilance in the form of an exposure registry and risk minimisation measures in the form of material to encourage healthcare professionals to enrol their patients in the registry as requested.
The full protocol was submitted in August 2016 and is currently under assessment.

The risk minimisation material can be subject to further national level modifications as required.

The overall benefit/risk balance is, therefore, considered to be positive.

**RECOMMENDATION**

The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and package leaflet is available on the MHRA website. The current labelling is presented below:
ANNEX 1-Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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