APPLICATION NUMBER:

209347Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)
NDA #: 209347  Supporting Document Numbers: 000

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  Revised label to comply with PLLR (SDN 007): August 2, 2016
  Response to filing letter deficiencies & draft labeling (SDN 008): September 9, 2016
  Revised label (SDN 012): November 28, 2016

Related/Supporting Documents: IND 117705, NDA 019661, DMF

Product Name(s):
  Proprietary: Ganciclovir Injection
  Non-Proprietary/USAN: Ganciclovir Injection
  Code Name/Number: 82410-32-0

Structural Formula:

Molecular Formula: C₉H₁₃N₅O₄
Molecular Weight: 255.23
Indication(s): For the treatment of HCMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Injection is also indicated for the prevention of HCMV disease in transplant recipients.

Dosage Form(s): Injectable (2 mg/mL)
Route(s) of Administration: Intravenous Infusion
Recommended Dosage: 5 mg/kg/day
Dispensed: Rx ___ OTC ____ (Discipline relevant)

Abbreviations: AIDS, acquired immune deficiency syndrome; CC, cytotoxic concentration; CDV, cidofovir; D+, donor CMV seropositive; EC, effective concentration; FOS, foscarnet; GCV, ganciclovir; HAART, highly active antiretroviral regimen; HCMV, human cytomegalovirus; HIV, human immunodeficiency virus; HSCT, stem-cell transplant; R-, recipient CMV seronegative; SOT, solid organ transplant; VGCV, valganciclovir;
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Reference ID: 4024441
EXECUTIVE SUMMARY

1. Recommendations

1.1. Recommendation and Conclusion on Approvability:
This 505 b(2) Original NDA is approvable from a Clinical Virology perspective for the treatment of HCMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Injection is also indicated for the prevention of HCMV disease in transplant recipients.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable:

2. Summary of OND Virology Assessments

2.1. Nonclinical Virology
The sponsor did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted with the Cytovene® and Valcyte® original NDA submissions (NDA 19661, SDN 000 and NDA 21304, SDN 000).

2.2. Clinical Virology
No new clinical data are included in support of the sponsor’s proposed drug product because the sponsor believes the changes that were made to their product do not affect the safety or efficacy of the drug product.

3. Administrative

3.1. Reviewer’s Signatures

_______________________________________
Takashi E. Komatsu, Ph.D., RAC
Clinical Virology Reviewer

3.2. Concurrence

_________________________________
HFD-530/Clin.Virol.TL/J. O’Rear, Ph.D.

CC:
HFD-530/NDA # 209347
HFD-530/Division File
HFD-530/PM/Martin-Yeboah
OND Virology Review

1. Introduction and Background

Cytomegaloviruses are members of the Herpesviridae family, and are capable of causing a variety of acute, latent and recurrent infections in humans and animals. HCMV, also designated as the human herpesvirus 5, is the prototype of the beta herpesvirus group (Roizman et al., 1981). Like other herpesviruses, HCMV is able to establish latent infections, which can subsequently recur to an active infection state. The HCMV genome is about \( \text{open reading frames} \).

Seroepidemiologic surveys have demonstrated HCMV infection in every population tested. The HCMV seroprevalence is estimated between 50% and 80% in the US (40% globally). The prevalence of HCMV infection increases with age and is higher in developing countries and among the lower socioeconomic groups in developed countries. Primary infection usually occurs during the first decades of life and humans are believed to be the only host of the virus. Transmission sources of HCMV include saliva, urine, semen, cervical and vaginal secretions, milk, stool, blood, cells, tissues, and organ transplants. Primary infection in immunocompetent subjects is mainly asymptomatic or it may be associated with a self-limited mononucleosis-like syndrome and leads to a life-long latency. However, HCMV infections are symptomatic and associated with increased morbidity and mortality in patients with immature or compromised immune systems. These groups of patients include congenitally infected newborns, patients with acquired immune deficiency syndrome (AIDS), and transplant recipients (hematopoietic stem cell and solid organ transplants). This review focuses primarily on the antiviral drugs and mechanism of drug resistance in the setting of HCMV infection of adults with compromised immune systems. Unfortunately, despite the major public health need (Dollard et al., 2007), no antiviral drugs are approved for the prevention or treatment of congenital HCMV infection.

HCMV is a common infection in patients with advanced HIV disease. In the era before the availability of highly active antiretroviral regimen (HAART), it was estimated that up to 45% of patients with AIDS acquired HCMV disease (Masur et al., 1996). HCMV retinitis is by far the most common manifestation of HCMV disease in AIDS patients, accounting for 85% of the cases (Gallant et al., 1992). However, the introduction of HAART has decreased the incidence of HCMV diseases in AIDS patients by more than 80% (Jabs et al., 2007). Currently approved drugs for the treatment of HCMV retinitis in HIV patients include intravenous ganciclovir, oral ganciclovir, ganciclovir intraocular implant, oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and intravenous fomiviren. The choice for the initial treatment of HCMV retinitis is based on the severity of the disease and other factors such as the ability to adhere to treatment. In most of the cases, oral valganciclovir is the preferred drug for initial treatment.

CytoVene® (ganciclovir, NDA 19661, link to label), a non-prodrug, injectable version of the active moiety of valganciclovir, was approved for the treatment of HCMV retinitis in adult subjects with AIDS in 1989. After uptake by cells infected with HCMV, ganciclovir is phosphorylated to the active moiety, ganciclovir triphosphate, by the virally encoded UL97 kinase and cellular kinases. Ganciclovir triphosphate is the active inhibitor of viral DNA synthesis catalyzed by the viral DNA polymerase pUL54.

The antiviral activity of GCV is dependent on its initial phosphorylation by the the virally encoded pUL97 kinase. Interestingly, the UL97 gene encodes amino acid sequence motifs characteristic of protein kinases, and has homologies with kinase genes in other herpesviruses (Michel and Mertens, 2004). Several pUL97 amino acid substitutions conferring resistance to GCV have been detected in clinical
isolates. Resistance can also develop by amino acid substitutions in the viral encoded pUL54 DNA polymerase.

Other Approved Drugs for HCMV

Valcyte® (valganciclovir hydrochloride tablets, NDA 21304, link to label) was approved for the treatment of human cytomegalovirus (HCMV) retinitis in adult subjects with AIDS in March, 2001. The indication for Valcyte® tablets was further expanded in September, 2003 to include the prevention of HCMV disease in adult solid organ transplant (SOT) patients. Valcyte® oral solution (valganciclovir hydrochloride) was approved on August 28, 2009 for the prevention of HCMV disease in pediatric kidney and heart transplant subjects ≥4 months of age at high risk of developing HCMV.

Valganciclovir is an L-valyl ester prodrug of ganciclovir. After oral administration, valganciclovir is rapidly absorbed and hydrolyzed to ganciclovir. The majority of the hydrolysis occurs during pre-systemic absorption, with only 1%-2% of the absorbed prodrug valganciclovir appearing as valganciclovir in the plasma, the remainder being found as ganciclovir.

Foscavir® (foscarnet, NDA 20068, link to label) was approved for treatment of HCMV retinitis in AIDS patients in 1991. Foscavir®, or foscarnet sodium, is the trisodium salt of phosphormophonic acid, a pyrophosphonate analogue and is the second drug approved for HCMV retinitis. Foscarnet (FOS) inhibits the activity of the viral DNA polymerase by binding to the pyrophosphate binding site and blocking cleavage of pyrophosphate from the terminal nucleoside triphosphate added to the growing DNA chain. FOS is considered second-line therapy, but is the preferred drug for patients who are failing GCV therapy, presumably due to viral resistance, or those who cannot be treated with GCV due to dose-limiting neutropenia or leucopenia (Razonable and Emery, 2004). In one study, FOS was compared to IV GCV as a preemptive therapy in a large, prospective, randomized, open-label study in HSCT patients. FOS and IV GCV were equally effective in prevention of CMV disease and mortality within 180 days of HSCT (Reusser et al., 2002). FOS has also been used in combination with IV GCV, each at half dose, and the combination was compared to IV GCV alone in SOT patients. The outcome was unfavorable for the combination in terms of virologic response and toxicities (Mattes et al., 2004).

Vistide® (cidofovir, NDA 20638, link to label) received US marketing approval in 1996 for treatment of HCMV retinitis in AIDS patients. CDV is available only as an IV formulation; its oral bioavailability is less than 5%. The intracellular half-life of CDV-DP is reported to be >24 hours, and antiviral activity in both animal models and in humans can be achieved with infrequent dosing (De Clercq and Holý, 2005). CDV is an acyclic cytidine nucleoside analog phosphate, and is a broad-spectrum antiviral agent with activity against both herpesviruses and other DNA viruses, such as adenovirus (De Clercq and Holý, 2005). Host kinases convert CDV to the active diphosphoryl form, and cidofovir diphosphate then acts as a competitive inhibitor of the viral DNA polymerase, causing premature chain termination in viral DNA synthesis.

Vitravene® (fosmivirsen, NDA 20961, link to label) is an antisense phosphorothioate oligonucleotide that blocks the replication of HCMV mRNA. It is 21 nucleotides long, comprised of a sequence that is complementary to the mRNA transcribed from the major immediate-early transcriptional unit of HCMV (Mulamba et al., 1998). It is used in the treatment of HCMV retinitis in immunocompromised patients, including those with AIDS. It was licensed by the FDA for HCMV in Aug 1998. Fomivirsen was the first antisense antiviral approved by the FDA. A human cytomegalovirus mutant that was isolated for resistance (10-fold) to fomivirsen (ISIS 2922) exhibited cross-resistance to a modified derivative of fomivirsen with an identical base sequence but little or no resistance to an oligonucleotide with an
unrelated sequence (Mulamba et al., 1998). No changes in the mutant’s DNA corresponding to the fomivirsen target sequence were found.

**Treatment Strategies for HCMV**

HCMV is the single most frequent pathogen in transplant patients contributing significantly both to patient morbidity and mortality. Because of the increased morbidity and mortality associated with HCMV infection in transplant patients, it has been recognized that prevention of HCMV infection may be a better strategy than treatment of established infection. Prophylactic therapy and preemptive therapy are the two major strategies used for prevention. Currently FDA-approved drugs for the treatment and/or prophylaxis of HCMV include valganciclovir (VGCV), ganciclovir (GCV), cidofovir (CDV), and foscarnet (FOS). Pre-emptive treatment and prophylaxis therapy using one or more of these drugs represent the main treatment strategies to prevent HCMV disease in solid organ transplant (SOT) or hematopoietic stem cell transplant subjects. The incidence of resistance to anti-HCMV drugs using either strategy is poorly characterized, especially for oral valganciclovir, and it is conceivable that the incidence of resistance may differ between the two strategies. With pre-emptive therapy, treatment is given in the setting of active HCMV replication measured by DNAemia. For prophylaxis therapy, lower doses of valganciclovir are used in the absence of HCMV replication, and the main concern relates to the risk of resistance development during episodes of low level DNAemia.

The sponsor’s proposed drug product has the same active ingredient, route of administration, and indications as Cytovene®. However, the sponsor’s drug product differs from Cytovene® with respect to the active ingredient concentration, dosage form, and excipients used. The active ingredient concentration of the Cytovene® is 500 mg ganciclovir per vial as the sodium salt whereas the sponsor’s formulation contains active ingredient concentration as 2.0 mg/mL, 500 mg/250 mL. The Cytovene® contains sodium hydroxide, equivalent to about sodium (to provide a pH of upon reconstitution) and water for injection (solvent) which is removed during lyophilizing, whereas the sponsor’s formulation contains sodium chloride and may contain sodium hydroxide and hydrochloric acid as pH adjusters and water for injection as solvent.

**2. Nonclinical Virology**

The sponsor did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted with the Cytovene® and Valcyte® original NDA submissions (NDA 19661, SDN 000 and NDA 21304, SDN 000).

**3. Clinical Virology**

No new clinical data are included in support of the sponsor’s proposed drug product because the sponsor believes the changes that were made to their product do not affect the safety or efficacy of the drug product.

**4. Conclusion**

This 505 b(2) Original NDA is approvable from a Clinical Virology perspective for the treatment of HCMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Injection is also indicated for the prevention of HCMV disease in transplant recipients.

**Microbiology Package Insert**

The words with strikethroughs are the text the sponsor was requested to delete and words in blue are recommended insertions. Of note, the label is based off of Cytovene® (NDA 19661; label) which does not include any of the resistance/cross-resistance information.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ganciclovir is an antiviral drug with activity against cytomegalovirus (CMV) [see Microbiology (12.4)].

12.4 Microbiology

Mechanism of Action

Ganciclovir is a synthetic analogue of 2′-deoxyguanosine, which inhibits replication of human CMV in cell culture and in vivo. In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of the viral DNA polymerase, pUL54, by ganciclovir triphosphate.

Antiviral Activity

The median concentration of ganciclovir that inhibits CMV replication (EC<sub>50</sub> value) in cell culture (laboratory strains or clinical isolates) has ranged from 0.08 to 13.6 micromolar (0.02 to 3.48 μg/mL). Ganciclovir inhibits mammalian cell proliferation (IC<sub>50</sub> value) in cell culture at higher concentrations ranging from 118 to 2840 micromolar (30 to 725 μg/mL). Bone marrow-derived colony-forming cells are more sensitive (IC<sub>50</sub> value = 0.1 to 2.7 micromolar (0.028 to 0.7 μg/mL)). The relationship between the antiviral activity in cell culture and clinical response has not been established.
Resistance

Cell Culture: CMV isolates with reduced susceptibility to ganciclovir have been selected in cell culture. Growth of CMV strains in the presence of ganciclovir resulted in the selection of amino acid substitutions in the viral protein kinase pUL97 and the viral DNA polymerase pUL54.

In vivo: Viruses resistant to ganciclovir can arise after prolonged treatment or prophylaxis with ganciclovir by selection of substitutions in pUL97 and/or pUL54. Limited clinical data are available on the development of clinical resistance to ganciclovir and many pathways to resistance likely exist. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with Ganciclovir Injection. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.
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/s/

TAKASHI E KOMATSU
12/12/2016

JULIAN J O REAR
12/13/2016