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EXECUTIVE SUMMARY

Herpetic keratitis remains the leading cause of corneal blindness in the United States (Biser, 2006). It is a recurrent infection caused predominantly by herpes simplex virus-type 1 (HSV-1), a double-stranded DNA virus. In the US, the herpes simplex virus (HSV) is responsible for approximately 20,000 new diagnoses and 28,000 reactivations of herpetic keratitis annually. Incidents of herpetic keratitis occur at an approximate rate of 8.4 per 100,000 people (Colin, 2007). For patients diagnosed with herpetic keratitis ulcers, receiving immediate treatment provides the best chance of controlling the extent of subepithelial and stromal scarring and reducing the likelihood of vision loss.

Prior to the Food and Drug Administration (FDA) approval of ganciclovir ophthalmic gel 0.15% (ZIRGAN™), patients with herpetic keratitis in the US had only one marketed option for treatment. This option was trifluridine, which has been approved since 1980. The mechanism of action of trifluridine is nonspecific in that it inhibits DNA synthesis not only in cells infected with the herpes virus, but also in healthy, dividing epithelial cells. As a result, patients using trifluridine can incur a risk of ocular epithelial toxicity, including retarded healing of the corneal epithelium and stroma, corneal epithelial dysplasia (Maudgal, 1983) or conjunctival scarring (Udell, 1985).

In contrast, ganciclovir does not interfere with the DNA synthesis or regeneration of healthy cells. This characteristic of ganciclovir, viral specificity, was central to the rationale for developing ZIRGAN. As a novel treatment for herpetic keratitis in the US, data from 4 clinical trials have shown the efficacy and safety of ZIRGAN to be excellent. Indeed, integrated results of these trials have shown that Zirgan, administered 5 times per day until the herpetic ulcer heals then 3 times per day for 7 days thereafter, is as effective as acyclovir 3% ophthalmic gel, the European standard of care, in treating acute herpetic keratitis. These comparative studies enrolled 377 patients with acute herpetic keratitis across multiple clinical investigative sites in Africa, Europe, and Asia. Across these 4 studies, the proportion of patients whose herpetic ulcers healed when treated with ganciclovir ophthalmic gel was 87% with median time to recovery of 7 days. Based on these data, provided by Laboratoires Théa along with over 10 years of postmarketing survellience data, Sirion made the decision to submit a New Drug Application (NDA) to the FDA for the approval of ZIRGAN in the US. ZIRGAN was approved for marketing by FDA and also granted an orphan drug designation.

This document reviews the both the development path and clinical evidence that support the efficacious and safe use of ZIRGAN in the treatment of acute herpetic keratitis. Widespread acceptance of ganciclovir ophthalmic gel 0.15% in the international medical community for over a decade and the rarity of related postmarketing adverse events further support this routine use of ZIRGAN.

PLACE IN THERAPY

Herpetic Keratitis

Herpetic keratitis is one of the leading causes of corneal opacification and infection-related vision loss in both the US and the industrialized world, as well as being one of the primary diseases resulting in corneal transplantation (Biser 2007, Colin 2007). There are 8 viruses in the Herpes viridae family that are pathogenic for humans: herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpes virus type 6 (HHV6), human herpes virus type 7 (HHV7), Epstein-Barr virus (EBV), and human herpes virus type 8 (HHV8). Of these, almost 60% of the US population demonstrate evidence of infection with HSV by 5 years of age (Biser, 2006). Most humans show serologic evidence of infection by middle age, and in the population 60 years of age and older, close to 100% show HSV in their trigeminal ganglia when autopsied (Guess, 2007). Further, approximately 1% of all infected patients develop ocular manifestations of the disease at some point in their lives (Colin 2007).

Table 1. Viruses of the Herpes Viridae Family – Pathogenic in Humans

Alpha Herpes viruses	Beta Herpes viruses	Gamma Herpes viruses
Herpes simplex virus type 1 - HSV1	Cytomegalovirus - CMV	Epstein-Barr virus - EBV
Herpes simplex virus type 2 - HSV2	Human herpes virus type 6 - HHV6	Human herpes virus type 8 - HHV8
Varicella-zoster virus - VZV	Human herpes virus type 7 - HHV7	

Herpes simplex virus (HSV is a double-stranded-DNA virus that invades host cells, replicates in the nuclei, and leads to cell death with lysis and release of viral particles. These particles, in turn, infect surrounding cells. HSV infection is widespread in all human populations, however, HSV has not changed appreciably as it has spread throughout the world. In the US, HSV is responsible for approximately 20,000 new diagnoses and 28,000 reactivations of herpetic keratitis annually. Additionally, herpes zoster (HZ) is estimated to afflict up to 20% of the world population, with 10% to 20% of those cases having ophthalmic involvement. Herpes simplex, in general, is slightly more prevalent in males, and the average age of clinical presentation is in the range of the latter fifties to the early sixties (Graham, 2009).

As mentioned before, approximately 1% of those infected with herpes have ocular manifestations, and 20,000 new cases of ocular herpes are diagnosed in the US each year (Colin, 2007). Ocular outbreaks of herpetic keratitis can be caused by either HSV or HZ. HSV has two closely related serotypes, HSV1 and HSV2, which have different but overlapping predilections for the site of infection. HSV1 is most often the cause of orofacial disease, while HSV2 is most often the cause of anogenital disease. Either type of HSV can cause disease in either location, and both HSV1 and HSV2 cause herpetic keratitis with apparently

indistinguishable characteristics (Chaney, 1983; Lafferty, 1987; Umene, 2000), though most ocular lesions are a result of HSV1 (Colin, 2007). Ocular expressions of HSV include blepharoconjunctivitis, epithelial and stromal keratitis, uveitis, and retinitis. In those who have a history of external ocular HSV infection, approximately one-fifth develop stromal keratitis, which is the most common blinding manifestation of HSV (Guess, 2007). Reports in the US of visual disability caused by herpetic keratitis are as high as 40%, and the risk of blindness increases with the number and severity of recurrences. Upon diagnosis, immediate treatment of herpetic epithelial ulcers is necessary if scarring and other more serious complications leading to blindness are to be limited (Colin, 2007).

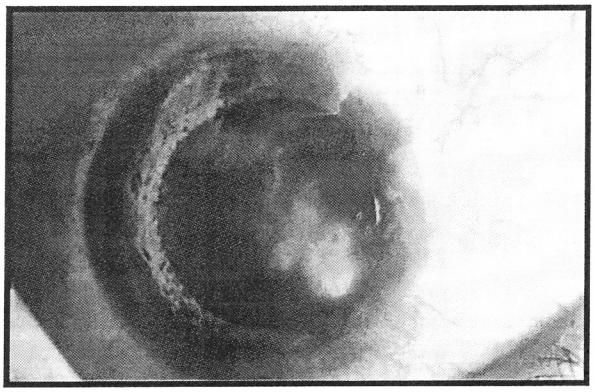


Photo 1: Dendritic Corneal Ulcer

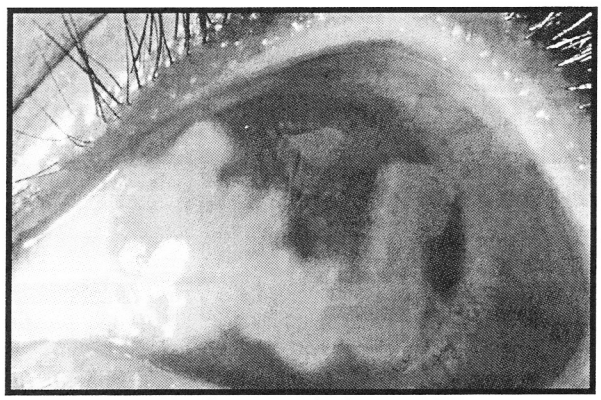


Photo 2: Geographic Corneal Ulcer

At presentation, corneal herpes infections begin as a cluster of small, clear vesicles in the epithelium that coalesce to form branching epithelial dendritic lesions that stain with fluorescein. Dendritic ulcers are present in approximately 15% of initial episodes of ocular HSV— disciform stromal keratitis makes up 2% of these cases (Kaufman, 2009). Dendritic ulcers can progress to geographic ulcers, a type of large epithelial defect with fimbriated edges. From this state, subsequent stromal involvement is possible. Epithelial keratitis is the most common form of ocular HSV disease, making up approximately 70% to 80% of all cases (Wilhelmus, 2007). With or without apparent clinical manifestations, after the initial infection, HSV becomes a lifelong, latent infection in the trigeminal ganglion or cornea. Recurrent episodes of ocular herpes increase over time: 9.6% at 1 year, 22.9% at 2 years, and 63.2% at 20 years (Miserocchi, 2007). With repeated outbreaks stromal involvement becomes common and the risk of blindness increases, caused by subsequent corneal scarring and uncontrolled intraocular inflammation. In fact, between 10% and 20% of patients with herpetic corneal ulceration go on to develop stromal immune keratitis, making them the greatest visual morbidity risk (Roy, 2006).

After the first infection, HSV typically becomes quiescent or latent in the trigeminal ganglion or the cornea. In this state, a variety of conditions, including stress, UV radiation, and hormone changes, can cause the virus to be reactivated. Herpetic infections have a tendency to re-occur in the cornea and uvea and may cause dendritic or geographic ulcers (Colin, 2007). Lesions also commonly occur when patients are immunosuppressed.

A summary of the treatment options available in the US for herpetic keratitis is reviewed later in this section.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA designates a drug product as an "Orphan Product" if the disease or condition for which the drug is used affects less than 200,000 people in the US.

Orphan Drug Designation in the US was granted to ZIRGAN on March 22, 2007 for the treatment of acute herpetic keratitis (dendritic and geographic ulcers).

Summary of Treatment Options in the United States

- Treatment for herpetic keratitis depends on both the manifestation and severity of the disease. Epithelial dendritic keratitis is most often treated with oral and/or topical antiviral therapy (Colin, 2007). Other than ZIRGAN, trifluridine (US trade name: Viroptic®) is the only antiviral agent currently approved for topical ocular herpes treatment. Although trifluridine is effective, its efficacy usually requires dosing up to 9 times per day (1 drop every 2 hours during the daytime). Moreover, it has the potential to cause ocular toxicity if administered for more than 21 days and its ocular penetration is poor if the corneal epithelium is intact (Colin, 1993). For a detailed comparison of ZIRGAN and Viroptic, see Table 2.
- Although not approved by FDA for this indication, oral acyclovir has been commonly prescribed to patients who are at high risk for toxicity from topical agents, patients who are immunocompromised, and pediatric patients. Often, patients on this regimen concurrently use an artificial tear product every 2 hours until the viral keratitis clears. Patients with frequent recurrences of ocular HSV are sometimes placed on a long-term regimen of oral antiviral medication at the prophylactic maintenance dose (Wang, 2009).
- Immune (inflammatory) stromal keratitis and endotheliitis are treated with combined corticosteroid and antiviral therapy. A topical steroid is prescribed and the antiviral medication is used concurrently to limit and prevent the virus replication cycle. The steroid is then titrated, based on clinical response, to the lowest dose necessary for managing the inflammation. A common recommendation is to use a topical antiviral agent and a corticosteroid with equal frequency until the steroid can be reduced to a once daily or less dosing regimen (Wang, 2009).

Surgical Care In Cases of Advanced Disease

Adequate management of ocular herpetic ulcers using topical antivirals can prevent the need for the surgical management options mentioned below:

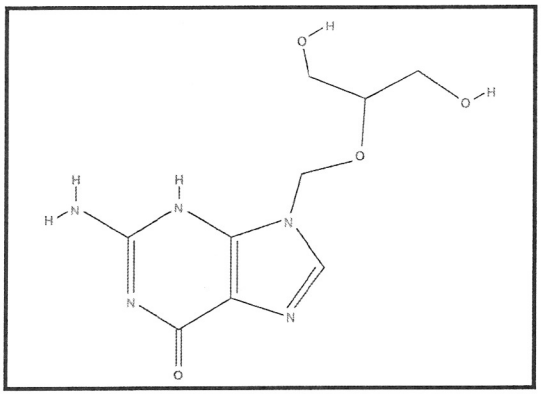
- Rigid gas-permeable contact lenses are sometimes used to correct irregular astigmatism resulting from chronic stromal keratitis
- Penetrating keratoplasty can be used for visual rehabilitation in patients with corneal opacities or corneal perforations
- Tissue adhesive, bandage contact lens, and/or amniotic membrane transplantation can sometimes be used to manage a small perforation in an inflamed eye

CHEMICAL PROPERTIES OF ZIRGAN

Chemistry

ZIRGAN is an ophthalmic gel formulation of ganciclovir 0.15% for topical instillation. Ganciclovir (9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl] guanine; Figure 1) is a synthetic guanine derivative antiviral drug that is active in vitro and in vivo against HSV.

Figure 1. Chemical Structure of Ganciclovir



As an ophthalmic aqueous gel formulation of ganciclovir, ZIRGAN provides sufficient contact time with the corneal surface to ensure therapeutic efficacy. Its aqueous formulation is better tolerated by patients than oil-based acyclovir ointment formulations, as demonstrated in both Phase 2b and Phase 3 trials. The gel formulation of ZIRGAN promotes a homogeneous distribution of the ganciclovir preparation and requires less frequent dosing than trifluridine.

The composition of ZIRGAN can be found in Table 2.

Table 2. ZIRGAN Quantitative and Qualitative Composition

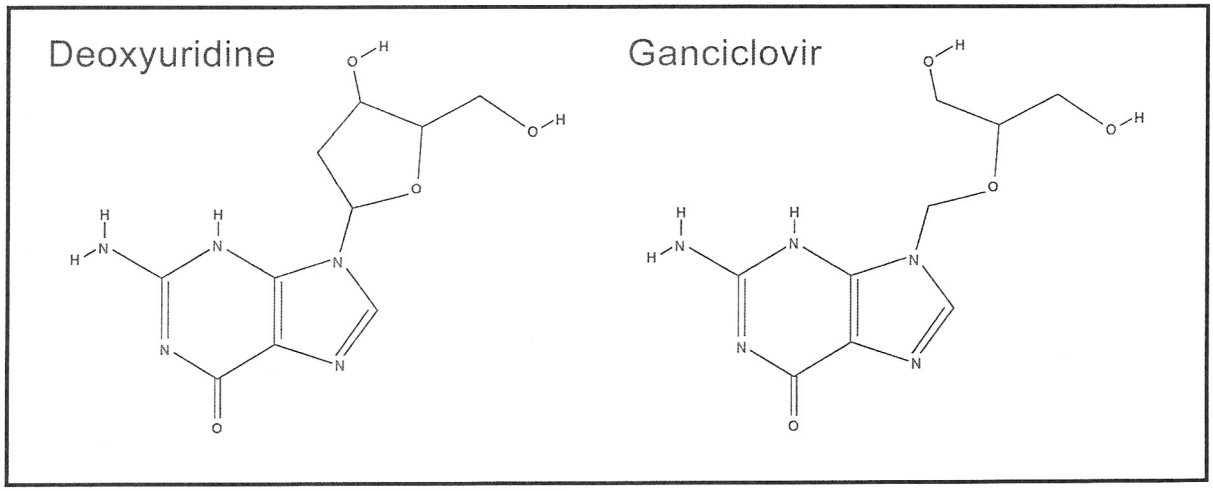
Component	Quantity (%w/w)	Function	Quality Standard
Ganciclovir	0.15%	Active ingredient	USP
Carbomer homopolymer	0.483%	Gelling agent	NF
Mannitol	5.00%	Tonicity agent	USP
Benzalkonium chloride 50% solution	0.015%	Antimicrobial preservative	USP/NF
Sodium hydroxide	As needed	pH adjustment	NF
Water for injection	qs	Aqueous vehicle	USP

NF, National Formulary; qs, quantum sufficient, a sufficient quantity; USP, United States Pharmacopeia

Mechanism of Action

Ganciclovir is a nucleoside analog of deoxyguanosine. As shown in Figure 2, the difference between the structures of ganciclovir and of deoxyguanosine is found in the deoxyribose. Ganciclovir lacks an actual deoxyribose, and instead has a deoxyribose-mimicking moiety. Like trifluridine, ganciclovir is phosphorylated prior to incorporation into DNA. However, the initial phosphorylation—which is essential for subsequent phosphorylations—can only be done by the viral thymidine kinase (vTK). Cellular TK does not recognize ganciclovir—the deoxyribose mimic does not work. The result is that ganciclovir passes into and out of uninfected normal cells with little effect at the doses used with ZIRGAN. However, in virus-infected cells phosphorylation by the vTK results in the creation of mono-phosphoganciclovir, which, being polar, is then trapped within virus-infected cells (Kitchington, 2005; Naesens, 2005). The selective phosphorylation of ganciclovir by vTK thus results in concentrations of ganciclovir triphosphate that are higher in the cells infected with herpes virus or adenovirus than in noninfected cells, targeting the drug's effects precisely to where it is needed. Ganciclovir monophosphate is then recognized by other cellular kinases, which create di- and tri-phosphoganciclovir. Triphosphoganciclovir is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA, slowing viral DNA synthesis in a manner similar to trifluridine. The more important mechanism of action, however, is that ganciclovir incorporation results in DNA chain termination—additional bases cannot be added to the phosphodeoxyribose backbone of DNA because ganciclovir lacks the deoxyribose needed (Hamzeh, 1990; Hayden, 2006; Ilsley, 1995).

Figure 2. Chemical Structures of Deoxyuridine and Ganciclovir



Trifluridine is the only other topical ophthalmic drug marketed in the US that is indicated for herpetic keratitis. Trifluridine is a close analog of thymidine, and it competitively inhibits the incorporation of thymidine into DNA. Trifluridine is itself incorporated into both viral and cellular DNA, where it interferes with base pairing and DNA function. Because cellular enzymes accept trifluridine as thymidine, the mechanism of action of trifluridine affects both cells infected by the virus and also healthy, dividing epithelial cells. As a result, patients

using trifluridine can incur a risk of ocular epithelial toxicity, including retarded healing of the corneal epithelium and stroma, corneal epithelial dysplasia (Maudgal, 1983) or conjunctival scarring (Udell, 1985).

Alternatively, ZIRGAN treats herpetic keratitis via a targeted mechanism of action that modifies only the cells infected with viral DNA. The onset of action of ZIRGAN is determined by the timing of the viral replication cycle so that, within minutes of application, the ganciclovir in ZIRGAN is available to interrupt and prevent the formation of new herpes virus DNA. (See Figure 3)

Figure 3. Mechanism of Action of Trifluridine and Ganciclovir