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Safety of Famciclovir in Patients with Herpes Zoster and Genital Herpes

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Safety reporting from individual ongoing and completed clinical studies has demonstrated that famciclovir, the well-absorbed oral form of the antiherpesvirus agent penciclovir, has been well tolerated by more than 3,000 individuals worldwide. An integrated safety evaluation has been performed and includes over 1,600 patients from 11 completed, randomized, double-blind clinical trials and 2 open trials. The famciclovir population consisted of 816 herpes zoster patients (four trials), 409 patients with acute genital herpesvirus infections (seven trials), and 382 patients from two genital herpes suppression studies. Overall, the famciclovir-treated patient population was 57.7% female and ranged in age from 15 to 102 years (mean, 42.6 years), with 31.2% aged 50 years or more and 15.7% aged 65 years or more. The mean duration of exposure to famciclovir was 28.8 days (5.8 days excluding suppression studies). The total daily doses ranged from 125 mg to 2.25 g. The most common adverse experiences reported as related to study medication (famciclovir and placebo) were headache, nausea, and diarrhea. The frequencies of adverse experiences and laboratory abnormalities (hematology, clinical chemistry, and urinalysis parameters) were similar in both famciclovir and placebo recipients. Thus, safety data from the analysis of 13 completed clinical studies demonstrate that famciclovir is tolerated well by patients with either herpes zoster or genital herpes and has a safety profile comparable to that of placebo.

Famciclovir is the well-absorbed (77% bioavailable) (9) oral form of penciclovir, a novel, selective antiviral agent with activity against varicella-zoster virus (VZV), herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), and Epstein-Barr virus (2, 16). Both the relative and absolute potencies of penciclovir and acyclovir are dependent on the host cell and assay method used, and inhibitory concentrations are generally comparable in vitro (1–3). However, the active triphosphate form of penciclovir has a prolonged intracellular half-life in both HSV (10 to 20 h)- and VZV-infected cells (9.1 h) compared with that of acyclovir triphosphate (≤1 h for both HSV- and VZV-infected cells) (4, 12, 15).

The most common adverse reactions reported in clinical studies with acyclovir include nausea and/or vomiting, diarrhea, headache, and rash (7). In addition, malaise was reported in patients who received acyclovir for herpes zoster (8). The safety and efficacy of famciclovir have been assessed in clinical trials of patients with herpes zoster and genital herpes (10, 11, 13). Safety reporting from individual ongoing and completed clinical studies demonstrate that famciclovir has been tolerated well by over 3,000 patients and volunteers worldwide. This report presents details of an integrated safety analysis covering 1,607 patients from 11 completed, randomized, double-blind clinical trails and two open studies.

Methodology. The safety of famciclovir was assessed in clinical studies of immunocompetent, adult patients with herpes zoster and genital herpes by recording adverse experiences and monitoring laboratory parameters. Adverse experiences were either identified by the investigator or elicited from the patient in response to the question, "Have you felt different in any way since starting the new treatment/the last assessment?" Details of each adverse experience (e.g., time of onset, duration, intensity, relationship to study medication, etc.) were recorded. For the analysis, adverse experiences were classified according to the World Health Organization coding system. Adverse experiences which were fatal, life threatening, disabling or incapacitating or which resulted in a new or prolonged hospitalization, a congenital anomaly, a carcinoma, or an overdose were classified as serious and are discussed separately, as are those events which led to withdrawal from the studies.

Samples for hematology, clinical chemistry, and urinalysis were obtained periodically in accordance with the protocol for each study (e.g., at baseline and during or upon completion of study medication). Any laboratory value considered to be clinically significant by the investigator was reported as an adverse experience. In addition, values which had changed from the baseline value by more than a specified amount and which were outside the sponsor-defined extended normal range were defined as values of potential clinical concern for the purpose of this safety evaluation. To detect overall changes, laboratory data were also examined by calculating the mean difference during treatment or within 7 days following completion of treatment from the pretreatment baseline (mean change from baseline).

Demographic characteristics. An integrated safety analysis has been completed for 1,607 patients participating in herpes zoster (816 patients) and genital herpes (791 patients) clinical studies. The majority of the herpes zoster patients (808) participated in three randomized, double-blind clinical studies. The remaining eight patients participated in an open-label famciclovir pharmacokinetic study. Seven genital herpes studies (six randomized, double-blind studies and one open label study) provided 409 patients who received famciclovir as acute therapy for the initial episodes or recurrent attacks of genital herpes infections, and 382 patients were treated for approxi-

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TABLE 1. Distribution of patients by total daily dose of famciclovir

Total daily dose (mg)	No. of Patients with:		Total no. of patients
	Herpes zoster	Genital herpes	
≥125	814	791	1,605
≥250	814	730	1,544
≥500	814	524	1,338
≥750	814	253	1,067
≥1,000	551	252	803
≥1,500	551	179	730
2,250	272	38	310

mately 4 months in two randomized, double-blind genital herpes suppression studies.

The mean duration of exposure to famciclovir for patients in the total patient population (herpes zoster and genital herpes) was 28.8 days (range, 1 to 173 days). Excluding the two genital herpes suppression studies, the mean duration of exposure to famciclovir was 5.8 days. The total daily dose of famciclovir for the 13 clinical studies under discussion ranged from 125 mg to 2.25 g, with approximately two-thirds of the patients receiving 750 mg or more of famciclovir daily. Distribution of patients by total daily dose of famciclovir is presented in Table 1. The mean cumulative dose of famciclovir was approximately 15 g, with a range of 125 mg to 86.5 g.

Famciclovir has been administered to a broad cross-section of the population with respect to age and sex because of the different diseases studied (i.e., herpes zoster and genital herpes). The mean age for famciclovir-treated patients was 42.6 years (range, 15 to 102 years), with 31.2% aged 50 years or more and 15.7% aged 65 years or more. As expected, participants in herpes zoster trials accounted for the majority of elderly patients. In this subpopulation, patients aged 50 years or more constituted 56.0% of the population, with 30.4% aged 65 years or more. In contrast, 94.4% of the participants in genital herpes studies were less than 50 years old. Females accounted for 57.7% of the overall patient population (64.1% of genital herpes population; 51.5% of herpes zoster population). More than 80% of the overall famciclovir-treated patient population was white; approximately 10% of the participants were black or of other ethnic origin.

Adverse experiences. The incidence and severity of adverse experiences reported as related to study medication administration (includes the categories of related, probably related, possibly related, and causalities which were unassessable or not indicated) were comparable between the famciclovir and placebo groups. Headache, nausea, and diarrhea were the most common adverse experiences reported. Headaches were reported in 9.3% of patients receiving famciclovir and 7.9% of patients receiving placebo. Nausea and diarrhea were less common, with 4.5 and 4.2% of patients reporting nausea and 2.4 and 2.3% reporting diarrhea in the famciclovir and placebo groups, respectively. All other adverse experiences occurred in <2% of the patient population. Table 2 summarizes the number of patients and incidence for adverse experiences occurring with a frequency of ≥1%.

Serious adverse experiences were reported for 1.8% of famciclovir-treated patients and 1.9% of patients who received placebo. None of the headache, nausea, or diarrhea episodes noted previously were classified as serious. In addition, no serious adverse experience in famciclovir-treated patients was reported as related or probably related to study medication administration. Similarly, no trends were observed in the occurrence of serious adverse experiences, since most of the events occurred only once. The overall withdrawal rates due to adverse experiences were similar in the famciclovir (2.4%) and placebo (1.6%) groups. The leading cause of withdrawal for famciclovir recipients was nausea (0.7%), whereas placebo recipients withdrew because of worsening of herpes zoster (0.5%). Adverse experiences leading to withdrawal that were considered to be related or probably related to study medication administration occurred in 0.5% of both the famciclovir and placebo patient populations. No deaths were attributed to treatment with famciclovir.

TABLE 2. Patients reporting adverse experiences related[a] to study medication in famciclovir patient trials

Adverse experience	No. (%) of patients in treatment group reporting adverse experience	
	Famciclovir	Placebo
Headache	150 (9.3)	34 (7.9)
Nausea	72 (4.5)	18 (4.2)
Diarrhea	39 (2.4)	10 (2.3)
Fatigue	24 (1.5)	6 (1.4)
Dizziness	20 (1.2)	7 (1.6)
Abdominal pain	19 (1.2)	3 (0.7)
Dyspepsia	18 (1.1)	7 (1.6)

[a] Includes categories of related, probably related, possibly related, and adverse experiences where the relationship was unassessable or not indicated. Of a total of 1,607 patients receiving famciclovir, 24.6% reported adverse experiences. Of a total of 428 patients receiving placebo, 19.9% reported adverse experiences.

The adverse experience profile for famciclovir did not vary considerably when the data were analyzed by duration of therapy and by condition under study. For example, headache, nausea, diarrhea, and fatigue were the most frequently reported adverse experiences for short-term studies (i.e., all trials except the two genital herpes suppression studies) and herpes zoster studies. The incidence of each adverse experience was comparable between the famciclovir and placebo groups in both subsets.

The control group for two of the three randomized, double-blind studies of patients with herpes zoster received acyclovir. Table 3 summarizes the numbers of famciclovir- and acyclovir-treated patients and incidences of adverse experiences for all events reported as related to study medication which occurred with a frequency of ≥1% in these two acyclovir-controlled studies. As with the overall famciclovir patient population, headache (6.0%) and nausea (3.7%) were the most frequently

TABLE 3. Patients reporting adverse experiences related[a] to study medication in acyclovir-controlled herpes zoster trials

Adverse experience	No. (%) of patients in treatment group reporting adverse experience	
	Famciclovir	Acyclovir
Headache	32 (6.0)	12 (4.6)
Nausea	20 (3.7)	7 (2.7)
Abdominal Pain	9 (1.7)	6 (2.3)
Diarrhea	7 (1.3)	5 (1.9)
Vomiting	6 (1.1)	1 (0.4)
Dizziness	6 (1.1)	2 (0.8)
Constipation	6 (1.1)	1 (0.4)
Fatigue	4 (0.7)	6 (2.3)
Anorexia	1 (0.2)	5 (1.9)

[a] Includes categories of related, probably related, possibly related, and adverse experiences where the relationship was unassessable or not indicated. Of a total of 535 patients receiving famciclovir, 21.1% reported adverse experiences. Of a total of 263 patients receiving acyclovir, 20.2% reported adverse experiences.

TABLE 4. Laboratory abnormalities

Laboratory variable[a]	% Patients in treatment group with laboratory abnormality	
	Famciclovir	Placebo
Hematology		
Hemoglobin	0	0
Platelets	0	0
Leukocytes	0.2	1.2
Liver function		
AST (SGOT)	0.7	0.5
ALT (SGPT)	1.4	1.2
Alkaline phosphatase	0.1	0.2
Total bilirubin	0.5	1.2
Albumin	0.1	0
Renal function		
Blood urea nitrogen	0	0.3
Serum creatinine	0	0.2
Chemistry		
Phosphate	2.5	1.5
Sodium	0.2	0
Potassium	0.1	0.2

[a] Abbreviations: AST, aspartate transaminase; SGOT, serum glutamic oxaloacetic transaminase; ALT, alanine transaminase; SGPT, serum glutamic pyruvic transaminase.

reported adverse experiences for famciclovir-treated patients. The most common adverse experiences reported for acyclovir-treated patients were headache (4.6%), nausea (2.7%), abdominal pain (2.3%), and fatigue (2.3%).

Laboratory assessments. There was no consistent association between treatment with famciclovir or duration of exposure to famciclovir and the incidence of laboratory abnormalities. Table 4 summarizes values of potential clinical concern for representative laboratory parameters. Less than 1% of the total patient population treated with famciclovir had values of potential clinical concern, with the exception of increases in alanine transaminase (1.4%) and serum phosphate (2.5%). In both cases, however, increases were also observed in alanine transaminase (1.2%) and serum phosphate (1.5%) for patients who received placebo.

Laboratory parameters related to hematology, hepatic function, renal function, serum electrolytes, muscle metabolism, bone metabolism, and glucose were examined for mean changes from baseline. No clinically significant differences between the famciclovir and placebo groups were observed. Similarly, famciclovir administration did not lead to any clinically relevant changes in urinalysis parameters.

Discussion. Biochemical studies on the mode of action of penciclovir (14) have shown that the preferential phosphorylation in herpesvirus-infected cells is even more marked for penciclovir than for acyclovir. The minimal phosphorylation of penciclovir in uninfected cells, together with the low activity of penciclovir triphosphate against cellular DNA polymerases, provides a rationale for the lack of toxicity of penciclovir in cell culture. This hypothesis has been tested in a wide range of human cell lines of differing tissue origin (2). These tests showed that penciclovir is like acyclovir in being exceptionally nontoxic to replicating cells in culture. Furthermore, evaluations of famciclovir and penciclovir in toxicological tests have shown that these compounds have a good safety profile, similar to that of acyclovir.

The ability of penciclovir triphosphate to inhibit DNA chain elongation was investigated in vitro. Under conditions designed to represent physiological concentrations of nucleoside triphosphates found within virus-infected cells in combination with penciclovir triphosphate or acyclovir triphosphate, penciclovir triphosphate (non-obligate chain terminator) was more effective than acyclovir triphosphate (obligate chain terminator) in inhibiting viral (HSV-2) DNA polymerase-mediated DNA chain elongation (4, 5, 14).

Famciclovir and acyclovir, with safety profiles comparable to that of placebo, are nucleoside analogs, a drug class which has been associated with adverse effects on testicular function. The potential for testicular effects was investigated in a study which included 67 men (34 famciclovir recipients and 33 placebo recipients) with recurrent genital herpes. Patients were randomized to receive either famciclovir (250 mg) or placebo twice daily for 18 weeks. Semen samples were provided every other week in the 8-week pretreatment period, during treatment, and in the 8-week posttreatment period. No significant effects of treatment were found upon proportions of dead, motile, or normal sperm or any other semen parameter, and famciclovir was tolerated well by study participants (10).

The favorable safety profile of famciclovir demonstrated by this integrated safety analysis is particularly noteworthy when viewed in relation to the current therapies available for the treatment of herpesvirus infections. Famciclovir is the only antiherpes agent other than acyclovir which exhibits a safety profile comparable to that of placebo both during short-term (5 to 7 days) and long-term (18 weeks) exposure. Ganciclovir, a nucleoside analog with a broad spectrum of activity against herpesviruses (HSV-1, HSV-2, VZV, cytomegalovirus, and Epstein-Barr virus), is considerably more toxic than either famciclovir or acyclovir and therefore is indicated primarily for the treatment of life- or sight-threatening cytomegalovirus-caused disease in immunocompromised patients (6). Similarly, foscarnet, a non-nucleoside analog with an in vitro spectrum of activity similar to that of ganciclovir, is limited in indication to the treatment of cytomegalovirus-caused retinitis in immunocompromised patients because of the potential for renal impairment.

The biochemical properties and safety profile of famciclovir favor its use for the treatment of herpesvirus infections, an area where treatment alternatives with acceptable safety profiles are limited. This integrated safety evaluation of over 1,600 patients who received famciclovir in 13 completed clinical studies of patients with herpes zoster or genital herpes demonstrates that famciclovir is tolerated well and exhibits a safety profile comparable to that of placebo.

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