

EMTALA Waiver Urged in Declared Emergency

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WASHINGTON — The Emergency Medical Treatment and Labor Act should be waived during declared emergencies, the statute's technical advisory group recommended to federal regulators late last year.

The exemption would apply during national, state, county, city, or hospital-specific situations, the panel agreed at a meeting held in Washington. EMTALA

imposes specific obligations on hospitals that participate in Medicare to treat emergency patients regardless of ability to pay.

In order to qualify for the proposed emergency-related exemption, a hospital would have to be directly experiencing the crisis, and the emergency must interfere with the hospital's ability to comply with EMTALA. In addition, a hospital would be required to take "reasonably practical steps" to secure care for patients by ensuring they are seen at another facility. Any

patient care decisions must apply to all patients regardless of insurance status.

Although Centers for Medicare and Medicaid Services (CMS) representatives said they were not aware of any hospitals being cited under EMTALA for not providing care during an emergency, the panel concluded that providers should not have to worry about possible violations under extreme circumstances.

The recommended waiver would preclude patients from filing lawsuits against

hospitals that could not provide care in an emergency situation, said panel member Brian Robinson, president and CEO of HCA Las Vegas. That would "allow hospitals and doctors to quite simply do the right thing for their patients at the time," he added.

In other action, the technical advisory group approved language that would affirm the use of technology in physician communications. The provision would replace current language in EMTALA guidelines that could be construed to prohibit the use of telemedicine devices.

The recommendation affirms that the treating physician has ultimate control over how a patient is treated, but that physicians may use a variety of methods to communicate with each other about patient care. It further indicates that an EMTALA violation occurs if an on-call physician refuses to physically appear at the emergency department when the treating physician requests it of him or her.

Panel members agreed that the use of technology should be encouraged to improve care in urban and rural settings.

"As we leverage technology to make a difference in how care is provided, we've got to ensure that there are no barriers to being able to utilize technology to improve patient care," said advisory group member Dr. Warren Jones, executive director of the Mississippi division of Medicaid.

The panel also agreed to disseminate a letter from CMS staff detailing when a hospital is responsible for a patient who arrives via emergency medical services. CMS staffer Dodgie Guioa said prior agency guidance on the issue was being used by EMS providers "as a weapon" to force hospitals to take patients as soon as they arrived, even if the facility did not immediately have enough capacity. "That was not the intent," he added.

EMS providers should stay with patients until resources are available to care for them, Mr. Guioa said. He added that it is not the intent of CMS to take enforcement actions against hospitals that cannot immediately take patients "if the circumstances are beyond their control."

The panel discussed a number of issues that will be decided at a later date. Those topics included improvements to the CMS EMTALA Web site and to EMTALA enforcement. Specifically, the panel is urging less variability by region in enforcement efforts, as well as improvements in surveyor training.

The issue of air ambulances also is under consideration. The group heard testimony indicating that hospitals sometimes refuse the services of specific air ambulance companies, insisting instead on the use of their own contractors.

The panel also is exploring whether psychiatric patients need a separate definition of emergency and whether there should be intermediate sanctions available for hospitals that potentially violate EMTALA.

Physician on-call issues remain a priority for the panel, including ways to encourage regionalization of services and to ensure that on-call specialists are available for needed care.

Famvir® (famciclovir)

Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Herpes Zoster: Famvir® (famciclovir) is indicated for the treatment of acute herpes zoster (shingles).

Herpes Simplex Infections: Famvir is indicated for:

- treatment or suppression of recurrent genital herpes in immunocompetent patients.
- treatment of recurrent herpes labialis (cold sores) in immunocompetent patients.
- treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famvir® (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Denavir® (penciclovir cream).

PRECAUTIONS

General

The efficacy of Famvir® (famciclovir) has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering Famvir to patients with creatinine clearance values <60 mL/min. (See **DOSAGE AND ADMINISTRATION** in the full prescribing information). In patients with underlying renal disease who have received inappropriately high doses of Famvir for their level of renal function, acute renal failure has been reported.

Famvir 125 mg, 250 mg and 500 mg tablets contain lactose (26.9 mg, 53.7 mg and 107.4 mg, respectively). Patients with rare hereditary problems of galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption should not take Famvir 125 mg, 250 mg and 500 mg tablets.

Information for Patients

Patients should be informed that Famvir is not a cure for genital herpes. There are no data evaluating whether Famvir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

There is no evidence that Famvir will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famvir should refrain from driving or operating machinery.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.1 to 4.5x the human systemic exposure at the recommended total daily oral dose ranging between 2000 mg and 500 mg, based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.7 to 2.7x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.3 to 1.2x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria (*S. typhimurium* and *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5,000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.4 to 5.7x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.15 to 0.6x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.3 to 1.2x the human AUC) and 150 mg/kg/day (1.3 to 5.1x the human AUC), respectively. Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (2.7 to 10.8x the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral Famvir (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8 week follow-up.

Pregnancy

Teratogenic Effects—Pregnancy Category B: Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 2.7 to 10.8x and 1.4 to 5.4x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (1.5 to 6x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.1 to 4.5x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.3 to 1.3x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.5 to 2.1x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Famvir, Novartis Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6682.

Nursing Mothers

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of Famvir in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with Famvir, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

Of 610 patients with recurrent herpes simplex (type 1 or type 2) in clinical studies who were treated with Famvir, 26 (4.3%) were ≥65 years of age and 7 (1.1%) were ≥75 years of age. Clinical studies of Famvir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In general, appropriate caution should be exercised in the administration and monitoring of FAMVIR in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of Famvir® (famciclovir) has been evaluated in clinical studies involving 816 Famvir-treated patients with herpes zoster (Famvir, 250 mg t.i.d. to 750 mg t.i.d.); 163 Famvir-treated patients with recurrent genital herpes (Famvir, 1000 mg b.i.d.); 1,197 patients with recurrent genital herpes treated with Famvir as suppressive therapy (125 mg q.d. to 250 mg t.i.d.) of which 570 patients received Famvir (open-labeled and/or double-blind) for at least 10 months; and 447 Famvir-treated patients with herpes labialis (Famvir, 1500 mg once or 750 mg b.i.d.). Table 5 lists selected adverse events.

Table 5
Selected Adverse Events (all grades and without regard to causality) Reported by
≥2% of Patients in Placebo-controlled Famvir® (famciclovir) Trials*

Event	Incidence							
	Herpes Zoster†		Recurrent Genital Herpes†		Genital Herpes-Suppression‡		Herpes Labialis‡	
	Famvir® 500 mg t.i.d.* (n=273) %	Placebo (n=146) %	Famvir® 1 gram b.i.d.* (n=163) %	Placebo (n=166) %	Famvir® 250 mg b.i.d.* (n=458) %	Placebo (n=63) %	Famvir® 1500 mg single dose* (n=227) %	Placebo (n=254) %
Nervous System								
Headache	22.7	17.8	13.5	5.4	39.3	42.9	9.7	6.7
Paresthesia	2.6	0.0	0.0	0.0	0.9	0.0	0.0	0.0
Migraine	0.7	0.7	0.6	0.6	3.1	0.0	0.0	0.0
Gastrointestinal								
Nausea	12.5	11.6	2.5	3.6	7.2	9.5	2.2	3.9
Diarrhea	7.7	4.8	4.9	1.2	9.0	9.5	1.8	0.8
Vomiting	4.8	3.4	1.2	0.6	3.1	1.6	0.0	0.0
Flatulence	1.5	0.7	0.6	0.0	4.8	1.6	0.0	0.0
Abdominal Pain	1.1	3.4	0.0	1.2	7.9	7.9	0.0	0.4
Body as a Whole								
Fatigue	4.4	3.4	0.6	0.0	4.8	3.2	1.3	0.4
Skin and Appendages								
Pruritus	3.7	2.7	0.0	0.6	2.2	0.0	0.0	0.0
Rash	0.4	0.7	0.0	0.0	3.3	1.6	0.0	0.0
Reproductive Female								
Dysmenorrhea	0.0	0.7	1.8	0.6	7.6	6.3	0.9	0.0

*Patients may have entered into more than one clinical trial.

†7 days of treatment

‡1 day of treatment

§daily treatment

The following adverse events have been reported during post-approval use of Famvir: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Table 6 lists selected laboratory abnormalities in genital herpes suppression trials.

Table 6
Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	Famvir® (n=660)† %	Placebo (n=210)† %
Anemia (<0.8 x NRL)	0.1	0.0
Leukopenia (<0.75 x NRL)	1.3	0.9
Neutropenia (<0.8 x NRL)	3.2	1.5
AST (SGOT) (>2 x NRH)	2.3	1.2
ALT (SGPT) (>2 x NRH)	3.2	1.5
Total Bilirubin (>1.5 x NRH)	1.9	1.2
Serum Creatinine (>1.5 x NRH)	0.2	0.3
Amylase (>1.5 x NRH)	1.5	1.9
Lipase (>1.5 x NRH)	4.9	4.7

*Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.

†n values represent the minimum number of patients assessed for each laboratory parameter.

NRH = Normal Range High.

NRL = Normal Range Low.

HIV-Infected Patients

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5x/day; n=143), respectively, were headache (16.7% vs. 15.4%), nausea (10.7% vs. 12.6%), diarrhea (6.7% vs. 10.5%), vomiting (4.7% vs. 3.5%), fatigue (4.0% vs. 2.1%), and abdominal pain (3.3% vs. 5.6%).

Post Marketing Experience

The following adverse events have been reported during post-approval use of Famvir: urticaria, serious skin reactions (e.g., erythema multiforme), jaundice, thrombocytopenia, hallucinations, dizziness, somnolence and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

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