Obtaining i.v. fosfomycin through an expanded-access protocol

Corey M. Frederick, Pharm.D., BCPS, Department of Pharmacy, Memorial Regional Hospital, Hollywood, FL.
Jennifer Burnette, Pharm.D., BCPS, Department of Pharmacy, Jackson Memorial Hospital, Miami, FL.
Laura Aragon, Pharm.D., BCPS (AQ–Infectious Diseases), Department of Pharmacy, Jackson Memorial Hospital, Miami, FL.
Timothy P. Gauthier, Pharm.D., BCPS (AQ–Infectious Diseases), Department of Pharmacy, Miami Veterans Affairs Healthcare System, Miami, FL.

Address correspondence to Dr. Frederick (corey.frederick26@gmail.com).

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NOTE

Purpose. One hospital’s experience with procuring i.v. fosfomycin via an expanded-access protocol to treat a panresistant infection is described.

Summary. In mid-2014, a patient at a tertiary care institution had an infection caused by a gram-negative pathogen expressing notable drug resistance. Once it was determined by the infectious diseases (ID) attending physician that i.v. fosfomycin was a possible treatment for this patient, the ID pharmacist began the process of drug procurement. The research and ID pharmacists completed an investigational new drug (IND) application, which required patient-specific details and contributions from the ID physician. After obtaining approval of the IND, an Internet search identified a product vendor in the United Kingdom, who was then contacted to begin the drug purchasing and acquisition processes. Authorization of the transaction required signatures from key senior hospital administrators, including the chief financial officer and the chief operating officer. Approximately 6 days after beginning the acquisition process, the research pharmacist arranged for the wholesaler to expedite product delivery. The ID pharmacist contacted the wholesaler’s shipping company at the U.S. Customs Office, providing relevant contact information to ensure that any unexpected circumstances could be quickly addressed. The product arrived at the U.S. Customs Office 8 days after beginning the acquisition process and was held in the U.S. Customs Office for 2 days. The patient received the first dose of i.v. fosfomycin 13 days after starting the expanded-access protocol process.

Conclusion. I.V. fosfomycin was successfully procured through an FDA expanded-access protocol by coordinating efforts among ID physicians, pharmacists, and hospital executives.

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The Food and Drug Administration (FDA) expanded-access and compassionate-use regulations enable clinicians to obtain treatments not currently approved for use in the United States for serious medical conditions. In the event that a needed medication is an investigational new drug (IND) under FDA review and the patient is ineligible for enrollment in ongoing clinical trials, the treatment may be made accessible through FDA. FDA highlights three distinct categories for expanded access: (1) individual patients, (2) intermediate-size patient populations, and (3) large patient populations. Furthermore, FDA differentiates between emergency and nonemergency patient access protocols.

Use of the protocol for the treatment of multidrug-resistant infectious pathogens is particularly noteworthy. As antimicrobial resistance has progressed, the drug development pipeline has been unable to meet clinical demands, particularly for gram-negative pathogens. This is exemplified by recent data that chronicled 599 carbapenem-resistant Enterobacteriaceae (CRE) cases across seven geographic metropolitan areas.
I.V. FOSFOMYCIN

NOTE

Product procurement

Once it was determined by the infectious diseases (ID) attending physician that i.v. fosfomycin was a possible treatment for our patient, the ID pharmacist began the process of drug procurement. This was a multistep process involving a variety of individuals.

The process began with the investigation of drug services (i.e., research) pharmacist and ID pharmacist reviewing specific information on the criteria for using the FDA expanded-access protocol. Subsequently, the research and ID pharmacists completed an IND application, which required patient-specific details and contributions from the ID physician. Components of an IND application include (1) a statement that the request is for an individual patient, (2) a brief clinical history, (3) a proposed treatment plan, (4) chemistry, manufacturing, pharmacology, toxicology, and controls information about the requested medication, (5) a copy of the signed informed-consent form, (6) a physician investigator qualification statement, and (7) FDA forms 1571 and 1572. Details including selection of the proposed dosing regimen were made by the ID physician in collaboration with the ID pharmacist after reviewing the product’s package insert. The IND application was submitted, and an emergency IND was granted by FDA later that day. In addition to the IND, FDA required the local institutional review board (IRB) to approve the use of the non-FDA-approved therapy. FDA requires a licensed physician treating the patient to serve as the principal investigator on the IRB application. FDA will only grant emergency IND approval and provide the approval number to the physician serving as the principal investigator. In addition, our institution-specific non-formulary-drug review assessed the drug’s safety, efficacy, and costs, with subsequent approval by pharmacy and therapeutics committee representatives (e.g., director of pharmacy, ID physician).

After obtaining approval of the IND, an Internet search identified a product vendor in the United Kingdom, who was then contacted to begin the drug purchasing and acquisition processes. Due to the lack of an existing vendor agreement to facilitate the anticipated transaction (i.e., for payment purposes), the ID and research pharmacists collaborated with the pharmacy business manager to obtain an emergency purchase order. The purchase order was necessary to ensure that payment would be provided to the new product vendor. During this process, the pharmacy business manager found that the manufacturer was not licensed to ship products to the United States, at which point a relationship with a wholesaler who could fulfill this role was established.

During this period, the pharmacy identified that the reimbursement potential was limited due to the drug’s nonapproved status. Drug acquisition cost was expected to exceed $10,000, based on financial calculations including purchasing price, shipping cost, and an expected 14-day duration of therapy. Authorization of the transaction required signatures from key senior hospital administrators, in-

KEY POINTS

- Utilization of the expanded-access protocol requires considerable coordination of resources in a timely manner.
- Identification of needed personnel and their corresponding responsibilities can allow for maximum efficiency when navigating the expanded-access protocol process.
- Through development of written protocols that deal with the expanded-access protocol process, hospitals can be ready for and respond to expanded-access protocol requests in a timely manner.

in 2012–13.4 The Centers for Disease Control and Prevention has identified CRE as an urgent threat to human health, with limited treatment options available in the United States.5 However, some agents and formulations not approved by FDA that are available in other countries, such as i.v. fosfomycin, have demonstrated clinical utility.6

This article describes our experience with obtaining i.v. fosfomycin via the FDA expanded-access protocol to raise awareness regarding the need to procure foreign non-FDA-approved treatments for patients infected domestically with drug-resistant pathogens.

Background

Fosfomycin, a broad-spectrum antibiotic with activity against both gram-negative and gram-positive organisms, has recently received increased interest due to its bactericidal activity in panresistant organisms.7 Although the drug was initially synthesized in 1969, it is available in the United States only as fosfomycin tromethamine, an oral formulation indicated for the treatment of urinary tract infections.8 Outside of the United States, i.v. fosfomycin is used to treat osteomyelitis, complicated urinary tract infections, nosocomial lower respiratory tract infections, and bacterial meningitis.9

In mid-2014, a patient at a tertiary care institution in Miami, Florida, had an infection caused by a gram-negative pathogen expressing notable drug resistance. The isolate was resistant to all antibiotics on our standard gram-negative sensitivity panel and was not susceptible to any other antibiotics tested by our microbiology laboratory. At that time, newly approved agents with retained susceptibility to CREs, such as ceftazidime–avibactam, had not received FDA-approved labeling. After review of potential antimicrobial agents to treat the patient’s infection, i.v. fosfomycin remained an option, and acquisition of the product was pursued.
In addition, the decision to pursue a non-FDA-approved medication for a patient is entirely dependent on the clinical case at hand. The following recommendations are provided for consideration by individuals who may be interested in pursuing procurement of a non-FDA-approved medication through FDA's expanded-access protocol.

**Identify existing institutional processes and personnel.** Identification of existing procedures and practices ahead of time will assist in detecting process gaps. If there is nothing in place or if the existing process requires substantial updates, establishing an institutional protocol that identifies key personnel and describes each person's responsibilities may be warranted. This protocol can be developed by key personnel likely to be involved in the process, including physician and pharmacy administrators. Such a resource will be invaluable should the process need to be initiated and navigated.

**Provide advance notice.** Given the complexity of the process and the number of steps involved, a proactive approach for informing personnel involved that a product has been requested is advisable whenever possible. This should happen in a logical sequence. The chief financial officer and other high-level administrators should be notified in a timely fashion; however, ensuring that the more fundamental tasks are underway first (e.g., drafting the IND application) is likely prudent.

**Evaluate costs early.** Products of this nature can incur large costs to the institution, and a patient's insurance may not provide reimbursement. For example, patients covered by Medicare and Medicaid cannot be billed for non-FDA-approved medications. If the insurer is a private organization, contacting the insurer in a timely fashion with an inquiry about opportunities for reimbursement is recommended.

**Identify the anticipated duration of therapy.** This is a component of the cost consideration, but positioning oneself in a way such that additional shipments will be required is not ideal. Alternatively, making a conservative purchase combined with a wait-and-see approach may be acceptable when the cost of therapy is high and the clinical course is uncertain. Weighing these options early on may be beneficial.

**Recognize time constraints.** Not all tasks are within the influence of those performing the majority of the required tasks. For example, our shipment was held in the U.S. Customs Office for two days. We subsequently learned that having the sender attach an external label to the package reading "emergent medical supply" would have helped expedite this part of the process. On the other hand, some processes may be more defined, especially if the agent being requested has a predefined expanded-access protocol (e.g., alemtuzumab). Recognizing these preexisting pathways may help expedite this process and exceed expectations regarding acquisition. Paying close attention to details such as these and maintaining communication are key but can be difficult when navigating such intricate processes.

**Conclusion**

I.V. fosfomycin was successfully procured through an FDA expanded-access protocol by coordinating efforts among ID physicians, pharmacists, and hospital executives.

**Disclosures**

The authors have declared no potential conflicts of interest.

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