



AMERICAN SOCIETY OF CLINICAL ONCOLOGY  
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## CLINICAL ALERT—LEUCOVORIN SHORTAGE

January 8, 2008

### **Why is there a shortage of leucovorin?**

There is currently a nationwide shortage of injectable racemic leucovorin, available only as a generic drug and only from two manufacturers in the US (Bedford Laboratories and Teva Pharmaceuticals). According to the FDA and the American Society of Health-System Pharmacists (ASHP), the companies have not provided information on how long this shortage, caused by unspecified "manufacturing delays," is expected to last.

### **What about using levoleucovorin?**

Levoleucovorin is the levo isomeric form of racemic (*d,l*)-leucovorin, and is the pharmacologically active isomer of leucovorin. Levoleucovorin is available under the brand name "Fusilev" (Spectrum Pharmaceuticals). According to the FDA website, limited supplies of levoleucovorin continue to be available (the ASHP does not list a shortage of this drug). Unlike leucovorin, levoleucovorin is not FDA-approved for use in colorectal cancer or other malignancies (with the exception of use for rescue after high-dose methotrexate therapy in osteosarcoma). However, it has been used off-label<sup>1</sup> in the treatment of malignancies, as a substitute for leucovorin, though noninferiority in terms of efficacy has not been tested either for metastatic disease or adjuvant therapy.

If clinicians and patients are considering the use of levoleucovorin, they should note the following:

- The dose for levoleucovorin is 50% of the usual dose of racemic leucovorin<sup>2</sup>
- Levoleucovorin is not FDA-approved for malignancy indications (except as noted above)
- The cost of levoleucovorin may be significantly higher than for leucovorin
- For the time being, you may wish to check with your Medicare contractor and private insurance carriers for coverage determinations.

The CMS **HCPCS code** for levoleucovorin is **J0641** (effective January 1, 2009). Please see the prescribing label for complete information.

(<http://www.fda.gov/cder/foi/label/2008/020140s001lbl.pdf>).

### **What about using oral leucovorin?**

According to the ASHP, leucovorin tablets are still available. Oral leucovorin is not FDA-approved for use in treatment of malignancies (except for methotrexate rescue in osteosarcoma), although its use has been evaluated in that setting.<sup>3</sup> The use of oral leucovorin may be limited by the large number of tablets needed and by the fact that oral absorption of leucovorin is saturable and highly variable.<sup>4,5</sup>

### **What about using capecitabine to substitute for the combination of 5FU/leucovorin?**

Capecitabine is an oral pro-drug of 5FU. For some treatment regimens, for some malignancies, substitution of capecitabine for the combination of 5FU/leucovorin is supported based on high quality randomized clinical trials. However, such data are not available for all 5FU/leucovorin containing regimens.

Capecitabine has been found to be noninferior to IV FU/leucovorin as single agents for both metastatic colorectal cancer and adjuvant therapy for stage III colon cancer.<sup>6,7,8</sup> In a large randomized phase III trial for patients with metastatic colorectal cancer, the combination of capecitabine and oxaliplatin was found to be noninferior to IV 5-FU/leucovorin and oxaliplatin (FOLFOX).<sup>9</sup> However, in the BICC-C trial, capecitabine and irinotecan (CAPIRI) was less efficacious and more toxic compared to IV 5-FU/leucovorin and irinotecan (FOLFIRI) at the doses of CAPIRI utilized in that trial.<sup>10</sup> No efficacy data are available from two trials testing capecitabine with oxaliplatin in the adjuvant therapy setting for colon cancer to date.

The side effect profile of capecitabine differs from that for 5FU/leucovorin (e.g. more hand-foot syndrome). When using capecitabine, issues such as patient compliance and gastrointestinal absorption also merit consideration. Complete prescribing information is available at: <http://www.fda.gov/cder/foi/label/2005/020896s016lbl.pdf>.

These decisions obviously need to be made by the treating physician in the context of individual patient circumstances.

### **What if I have patients enrolled in clinical trials using leucovorin?**

You should contact the study sponsor for instructions on how to proceed.

### **What can the FDA do?**

If shortages are projected to last for several weeks or months, the FDA has authority to investigate alternative sources of leucovorin, including foreign manufacturers. The FDA may also temporarily designate alternative drugs as acceptable but has not done so as of yet.

### **What can CMS do?**

ASCO has made CMS aware of this shortage and is advocating for coverage of appropriate alternatives during this shortage.

### **What is ASCO doing to assist members?**

ASCO is working with the FDA and CMS to identify and address issues that may surface as providers implement alternative treatment plans during this shortage. Specifically, ASCO will let members know when adequate supplies are expected. We will provide updates as new information becomes available from the manufacturers, FDA, CMS and other insurers. If you have questions, please contact us at [policy@asco.org](mailto:policy@asco.org).

***This alert is not medical or reimbursement advice or ASCO clinical guidance. Physicians should exercise professional clinical judgment in treating individual patients.***

### **Additional Resources**

American Hospital Formulary Service (AHFS) Drug Information® Off-label Use Determinations. Levoleucovorin, August 2008. Available at [http://www.ahfsdruginformation.com/off\\_label/tables/determination\\_levoleucovorin.pdf](http://www.ahfsdruginformation.com/off_label/tables/determination_levoleucovorin.pdf).

AHFS Drug Information®. Leucovorin Calcium Monograph. Available at ASHP website: <http://www.ashp.org/mngrphs/ahfs/a382336.htm>

ASHP Bulletin, Leucovorin Injection (Drug Shortages). Available at <http://www.ashp.org/Import/PRACTICEANDPOLICY/PracticeResourceCenters/DrugShortages/GettingStarted/CurrentShortages/Bulletin.aspx?id=488#ref>

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<sup>1</sup> See ASHP Bulletin, available at <http://www.ashp.org/Import/PRACTICEANDPOLICY/PracticeResourceCenters/DrugShortages/GettingStarted/CurrentShortages/Bulletin.aspx?id=488>

<sup>2</sup> Refer to full prescribing label and also see ASHP Bulletin.

<sup>3</sup> Goldberg RM, Hatfield AK, Kahn M, et al. Prospectively randomized North Central Cancer Treatment Group trial of intensive-course fluorouracil combined with the l-isomer of intravenous leucovorin, oral leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. *J Clin Oncol*. 1997;15(11):3320-3329.

<sup>4</sup> AHFS Drug Information, Leucovorin Calcium Monograph. Selected revisions July 2006. Available at <http://www.ashp.org/mngrphs/ahfs/a382336.htm>

<sup>5</sup> US Food and Drug Administration, Center for Drug Evaluation and Research. FDA Oncology Tools Product Label Details in Conventional Order for Leucovorin. September 2000. Available at <http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=leucovorin>

<sup>6</sup> Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; 19:4097-106

<sup>7</sup> Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; 19:2282-92

<sup>8</sup> Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005 Jun 30;352(26):2696-704

<sup>9</sup> Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008 Apr 20;26(12):2006-12

<sup>10</sup> Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C study. *J Clin Oncol* 2007 Oct 20;25(30):4779-86

The American Society of Clinical Oncology (ASCO) is the world's leading professional organization representing physicians who care for people with cancer. With more than 25,000 members, ASCO is committed to improving cancer care through scientific meetings, educational programs and peer-reviewed journals. For ASCO information and resources, visit [www.asco.org/presscenter](http://www.asco.org/presscenter). Patient-oriented cancer information is available at [www.cancer.net](http://www.cancer.net).