

Off-label uses included in the table represent only those uses that have submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

| Off-label Use (condition and patient population) | Regimen | Strength of Evidence; Strength of Study End Point (s) | Grade of Recommendation | Disclosure Information | AHFS Publication Date |
|---|--|--|-------------------------|---|-----------------------|
| First-line therapy for advanced-stage colorectal cancer | Levoleucovorin 100 mg/m ² as an IV injection, followed by fluorouracil 400 mg/m ² as a 2-hour IV infusion; both drugs given daily on days 1-5 with dosage adjustments, as needed, for response and/or toxicity. ¹ Cycle repeated every 4 weeks | High quality (see Clinical Trial Summary) End point: Survival | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |
| First-line therapy for advanced-stage colorectal cancer | Levoleucovorin 100 mg/m ² as an IV injection, followed by fluorouracil 370 mg/m ² by IV injection; both drugs given daily on days 1-5 with dosage adjustments, as needed, for response and/or toxicity. ² Cycle repeated at 4 and 8 weeks, then every 5 weeks thereafter | High quality (see Clinical Trial Summary) End point: Survival | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |
| First-line therapy for advanced-stage colorectal cancer | <i>Biweekly or Simplified LV5FU2 (sLV5FU2)³</i> Levoleucovorin 200 mg/m ² as a 2-hour IV infusion on day 1; followed by fluorouracil 400 mg/m ² as an IV injection on day 1, then 1500 mg/m ² /day as a continuous IV infusion over 23 hours on days 1 and 2 (a total of 3000 mg/m ² by continuous IV infusion over 46 hours) with dosage adjustments, as needed, for response and/or toxicity. Cycle repeated every 2 weeks | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |

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| First-line therapy for advanced-stage colorectal cancer | <p><i>FOLFOX4 Regimen³</i></p> <p>Oxaliplatin 85 mg/m² as a 2-hour IV infusion on day 1; levoleucovorin 100 mg/m² as a 2-hour IV infusion on days 1 and 2; followed by fluorouracil 400 mg/m² as an IV injection, on days 1 and 2, then 600 mg/m²/day as a continuous IV infusion on days 1 and 2 (a total of 1200 mg/m² by continuous IV infusion over 44 hours) with dosage adjustments, as needed, for response and/or toxicity.</p> <p>Cycle repeated every 2 weeks</p> | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |
| First-line therapy for advanced-stage colorectal cancer | <p><i>FOLFOX6 Regimen⁴</i></p> <p>Levoleucovorin 200 mg/m² as a 2-hour IV infusion on day 1; oxaliplatin 100 mg/m² as a 2-hour IV infusion on day 1; followed by fluorouracil 400 mg/m² as an IV injection on day 1, then 1200 mg/m²/day as a continuous IV infusion over 23 hours on days 1 and 2 (a total of 2400 mg/m² by continuous IV infusion over 46 hours) with dosage adjustments, as needed, for response and/or toxicity.</p> <p>Cycle repeated every 2 weeks</p> | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |
| First-line therapy for advanced-stage colorectal cancer | <p><i>Modified FOLFOX6 (or modified de Gramont) Regimen^{5,6}</i></p> <p>Levoleucovorin 175 mg as a 2-hour IV infusion; oxaliplatin 85 mg/m² as a 2-hour IV infusion on day 1; followed by fluorouracil 400 mg/m² as an IV injection on day 1, then 1200 mg/m²/day as a continuous IV infusion over 23 hours on days 1 and 2 (a total of 2400 mg/m² by continuous IV infusion over 46 hours) with dosage adjustments, as needed, for response and/or toxicity.</p> <p>Cycle repeated every 2 weeks</p> | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |

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| First-line therapy for advanced-stage colorectal cancer | <i>FOLFOX7 Regimen</i> ³ Levoleucovorin 200 mg/m ² as a 2-hour IV infusion on day 1; oxaliplatin 130 mg/m ² as a 2-hour IV infusion on day 1; followed by fluorouracil 1200 mg/m ² /day as a continuous IV infusion over 23 hours on days 1 and 2 (a total of 2400 mg/m ² by continuous IV infusion over 46 hours) with dosage adjustments, as needed, for response and/or toxicity. Cycle repeated every 2 weeks | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |
| First-line therapy for advanced-stage colorectal cancer | <i>FOLFIRI Regimen</i> ⁴ Levoleucovorin 200 mg/m ² as a 2-hour IV infusion on day 1; irinotecan 180 mg/m ² as a 90 minute IV infusion on day 1; followed by fluorouracil 400 mg/m ² as an IV injection, then 1200 mg/m ² /day as a continuous IV infusion over 23 hours on days 1 and 2 (a total of 2400 mg/m ² by continuous IV infusion over 46 hours) with dosage adjustments, as needed, for response and/or toxicity. Cycle repeated every 2 weeks | Low quality (see Clinical Trial Summary) | Not fully established | No conflicts of interest were disclosed during this review. | August 2008 |

Clinical Trial Summary:

Levoleucovorin and Fluorouracil as first-line therapy for advanced-stage (metastatic) colorectal cancer

Levoleucovorin [(l)-leucovorin] was compared with racemic leucovorin ([dl]-leucovorin), in combination with fluorouracil in a phase 3, open-label, randomized study (n=248) to determine if a twofold increase in leucovorin dose would result in differences in overall response rate, toxicity, and survival for patients with metastatic and/or recurrent colorectal cancer.¹

- Patients were randomized to receive either levoleucovorin or racemic leucovorin, both dosed at 100 mg/m² and administered as an IV injection. The fluorouracil regimen was identical in both treatment groups.
- A slight improvement in overall response rates was reported for the levoleucovorin arm compared with the racemic leucovorin group (overall response rate: 32 versus 25%; complete response + partial response: 5 + 27% versus 3 + 21%, respectively).

- The discontinuance rates were similar (34% for both groups); severe adverse events were reported as 18% in the racemic leucovorin group compared with 13% in the levoleucovorin group. An increase in granulocytopenia (all grades) and grade III/IV leukopenia and diarrhea was reported in the racemic leucovorin group compared with levoleucovorin (increased toxicities with racemic leucovorin were granulocytopenia [all grades] 16%; grade III/IV granulocytopenia 6%; grade III/IV leukopenia 5%; and grade III/IV diarrhea 3%). The incidence of both grade I/II stomatitis and diarrhea was similar for both groups.
- An improvement in time-to-progression was reported with the levoleucovorin group (8 versus 6.25 months [p=0.0505]); however, no statistically significant difference was observed between the two treatment groups in overall survival (14.5 versus 15 months [p=0.28]), 1-year survival (58.3 versus 60.6% [p=0.72]), or estimated 2-year survival (15.3 versus 23% [p=0.16]).

A second phase 3, open-label, randomized study (n=926) evaluated equipotent doses of levoleucovorin compared with racemic leucovorin, administered either orally or IV in patients with advanced-stage (i.e., unresectable) colorectal cancer.²

- The study was designed to determine if the use of levoleucovorin would result in enhanced fluorouracil modulation, reflected as an improvement either in response rate or overall survival. The study was powered to detect a 25% reduction in mortality in the experimental arm (i.e., levoleucovorin) compared with racemic leucovorin.
- Patients were randomized to one of the following three treatment arms: levoleucovorin 100 mg/m² given as an IV injection, oral racemic leucovorin 125 mg/m² given at hours 0, 1, 2, and 3, or racemic leucovorin 200 mg/m² given by IV injection. The fluorouracil regimen was identical in all three treatment groups.
- A small increase in stomatitis and sepsis was reported in the IV racemic leucovorin group compared with the IV levoleucovorin group (increases in the racemic leucovorin group relative to levoleucovorin were: stomatitis: grade III/IV 3 and 2.6%, respectively; sepsis: grade III/IV: 2.3 and 0.6%, respectively). A variable pattern was reported for diarrhea, with a 2.7% increase and a 4% decrease in grade III and grade IV events, respectively in the IV racemic leucovorin arm. Three infection-related fatalities each were reported in the IV levoleucovorin and IV racemic leucovorin arms.
- The overall response rate reported was not statistically different between the three groups (28, 34 and 34% for IV levoleucovorin, and oral and IV leucovorin, respectively [p=0.31]); 1-year survival was approximately 40% for all treatment groups based on Kaplan-Meier survival curve estimates.

In a third study, either IV levoleucovorin or racemic leucovorin, in combination with fluorouracil (administered as a continuous IV infusion) were used as part of the simplified de Gramont regimen (i.e., sLVFU2) as one of the treatment regimens in the OPTIMOX1 protocol (a study that evaluated alternative dosing sequences and regimens to reduce the incidence of oxaliplatin-induced sensory neuropathy).³

- Patients received either IV levoleucovorin or racemic leucovorin; however, no information is provided in the methodology section indicating the rationale for selection between the levoleucovorin or racemic leucovorin regimens.
- The results, reported as both response and toxicity rates, reflected the different treatment sequence schedules; however, neither the response nor toxicity data are specifically described for the different leucovorin formulations.

Levoleucovorin with FOLFOX and FOLFIRI regimens as first-line therapy for advanced-stage colorectal cancer.

Randomized studies evaluating different schedules of various FOLFOX regimens (i.e., FOLFOX6, modified FOLFOX6, and FOLFOX7), as well as the FOLFIRI regimen, have reported using either IV levoleucovorin or racemic leucovorin for patients enrolled in these studies.^{3,4,5}

- Patients received either IV levoleucovorin or IV racemic leucovorin; however, no information is provided in the methodology section indicating the rationale for the selection of either the levoleucovorin or racemic leucovorin regimen.
- The results, reported as both response and toxicity rates, reflected the different treatment sequence schedules; however, neither the response nor toxicity data is specifically described for the different leucovorin formulations.

The FOCUS (fluorouracil, oxaliplatin, and CPT11–Use and Sequencing) study, conducted by the United Kingdom Medical Research Council (MRC), used levoleucovorin (levofolinate) exclusively, as part of the fluorouracil, irinotecan, and oxaliplatin-based regimens in this protocol.⁶ The safety and

response data reported in this study reflect the various chemotherapy sequences and combinations, administered either as first or second-line therapy for poor prognosis colorectal cancer patients; however, the specific effects attributed to levoleucovorin are not fully characterized.

Discussion:

Background

The use of leucovorin to enhance the cytotoxic effects of fluorouracil is a recognized treatment for advanced-stage colorectal cancer.⁷ Racemic leucovorin (containing a mixture of both the levo [*l*] and dextro [*d*] stereoisomers), administered either orally or as an IV infusion, is the formulation that has been used in the US since 1952.⁸ It is recognized that the *l*-isomer (levoleucovorin) is the biologically active form of leucovorin and exhibits a different pharmacokinetic profile to that of the *d*-isomer, characterized by enhanced absorption following oral administration, a more rapid metabolism or transformation to the active 5-methyltetrahydrofolate (5-MTHF) metabolite, and a reduced fraction excreted by renal elimination.⁹ Despite the long-term use of the racemic leucovorin formulation, concerns have been raised about the potential effects of the *d*-isomer on the absorption and disposition of the *l*-isomer.⁹ Proposed pharmacokinetic interactions between the two isomers include competitive inhibition of the intracellular transport process, inhibition of polyglutamation, and changes in plasma protein binding, thereby modifying the renal clearance or filtration of the *l*-isomer, resulting in increased renal elimination of the active metabolite.⁹ However, pharmacokinetic data from small clinical studies conducted in both healthy individuals and cancer patients have failed to confirm the adverse effects of the *d*-isomer on the biologically active moiety when the oral racemic leucovorin formulation is used.^{9,10}

Administration of racemic leucovorin by the IV route bypasses the first-pass metabolism and saturable oral absorption – two stereoselective processes resulting in enhanced bioavailability of the *d*-isomer. Therefore, administration of high doses may result in elevated serum concentrations of the *d*-isomer, thereby modifying the activity of the *l*-isomer.⁹ Data from two studies, conducted with both healthy individuals and colorectal cancer patients, showed no inhibitory effects on the *l*-isomer pharmacokinetic profile when IV racemic leucovorin was given either prior to or concurrently with an equipotent dose of IV levoleucovorin.^{11,12} However, a cross-study analysis performed on a small number of colorectal cancer patients receiving equipotent IV doses of levoleucovorin reported higher levels of the parent compound and lower levels of the active metabolite (5-MTHF) with levoleucovorin compared with the racemic leucovorin formulation.¹³ Another small study characterized the potential pharmacokinetic interactions at a cellular level for both the levo- and racemic leucovorin forms by evaluating tumor concentrations of both isomers in liver metastases in patients with colorectal cancer.¹⁴ These investigators reported higher tumor-to-serum ratios in patients receiving levoleucovorin compared with the racemic leucovorin form, suggesting a possible inhibitory effect of the *d*-isomer in preventing adequate cellular uptake of the active *l*-isomer in tumors. The clinical importance of the results described in these *in vitro* studies is not fully known.

Summary:

Levoleucovorin is currently FDA-approved for use after high-dose methotrexate therapy in patients with osteosarcoma, and to diminish the toxicity and counteract the effects of impaired methotrexate elimination or inadvertent overdose of folic acid antagonists.⁷ The approved dosage for this indication is 7.5 mg (as a fixed dose) every 6 hours for a total of 10 doses, starting 24 hours after the beginning of the methotrexate infusion. The dosages proposed with the off-label fluorouracil-containing regimens in adults with metastatic colorectal cancer range from 100-200 mg/m² for each dose.^{1,2,3,4,5,6} These doses reflect a 50% reduction of the racemic leucovorin dose based on data from a bioequivalence study confirming similar serum concentrations of both 5-MTHF and total tetrahydrofolate following either an oral or IV dose.¹⁵

Results from the randomized studies revealed a slight reduction in grade III/IV toxicity (i.e., diarrhea, stomatitis, leukopenia, and sepsis-related events) with levoleucovorin compared with the racemic leucovorin formulation. In one study, it was concluded that there were no differences in toxicity between levoleucovorin and racemic leucovorin when used with fluorouracil;² however, in another study, the investigators reported an increase in granulocytopenia with racemic leucovorin, but acknowledged that due to the lack of complications (e.g., febrile/neutropenic events) and the low incidence

of granulocytopenia overall for the study population, the observed increase may be of limited importance.¹ Levoleucovorin has been used safely and effectively outside the US as part of an oxaliplatin or irinotecan-containing regimen (i.e., FOLFOX or FOLFIRI),^{3,4,5,6} however, data are not available from randomized studies directly comparing the safety and efficacy of levoleucovorin with racemic leucovorin in such regimens. Published data describing the use of levoleucovorin as part of a fluorouracil-based regimen (i.e., FOLFOX or FOLFIRI) with bevacizumab are not available; therefore, the safety profile has not been fully established for use with such combinations.

Given the lack of established difference in either the safety or efficacy profile of the levoleucovorin-fluorouracil regimens relative to the racemic leucovorin-fluorouracil regimens, as well as the lack of consistent pharmacokinetic data demonstrating an adverse effect of the racemic leucovorin formulation on the pharmacokinetics and biologic effects of the *l*-isomer, the clinical benefit of using levoleucovorin in combination with fluorouracil for the treatment of advanced-stage colorectal cancer is not fully established.

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