

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**8-107/S-054**

**Medical Review(s)**

**MEDICAL OFFICER REVIEW  
SUPPLEMENT  
(ADDITIONAL LABELING CHANGE)**

NDA: 8-107 (S-54; dated 10/27/2000)

DRUG: Leucovorin calcium injection/5-Fluorouracil  
in Colorectal Cancer Claim

SPONSOR: Immunex  
51 University St.  
Seattle, Washington 98101

In the DOSAGE AND ADMINISTRATION section, advanced Colorectal Cancer subsection, last paragraph, the following statement is made:

"Several other doses and schedules of leucovorin/5-fluorouracil therapy have also been evaluated in patients with advanced colorectal cancer; some of these alternative regimens may also have efficacy in the treatment of this disease. However, further clinical research will be required to confirm the safety and effectiveness of these alternative leucovorin/5-fluorouracil treatment regimens."

The other schedules of leucovorin/5-fluorouracil therapy, which were of interest at the time 5-FU/LV was approved for the 1<sup>st</sup>-line treatment of advanced colorectal, have been evaluated in randomized controlled trials. With survival as the endpoint of interest, the a summary of the results are in the table below.

| REGIMEN   | # OF ARMS WITH STATISTICALLY SIGNIFICANT INCREASE IN SURVIVAL VS. COMPARATOR    | # RCT TRIALS  | CANDIDATE AS NON-INFERIORITY COMPARATOR |
|---|---|---|---|
| 5-FU x 5d + LV x 5d<br>q 4 wks<br><br>(Mayo Clinic) | 6<br><br>won with low & high dose LV<br><br>won against MTX → 5-FU <sup>1</sup> | 9<br>references <sup>2 3 4 5 6 7 8</sup><br><sup>9 10</sup><br>, ,<br>, , | Yes                                     |

<sup>1</sup> Poon MA et al. Biochemical modulation of fluorouracil with leucovorin: Confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol. 1991; 9:1967-1972.

<sup>2</sup> J Clin Oncol. 1988;6:469-475

<sup>3</sup> J Clin Oncol. 1989;7:1407-1417

| REGIMEN   | # OF ARMS WITH STATISTICALLY SIGNIFICANT INCREASE IN SURVIVAL VS. COMPARATOR | # RCT TRIALS   | CANDIDATE AS NON-INFERIORITY COMPARATOR |
|---|--|--|---|
| 5-FU wkly + high-dose LV wkly<br><br>(Roswell Park) | 0<br><br>lost in a trial when Mayo Clinic 5-FU/LV lost against 5-FU          | 6<br>references <sup>11 12 13 14</sup> ,<br><sup>15 16</sup> , | NO                                      |
| 5-FU CI   | 0  | 5<br>references <sup>17 18 19 20</sup> ,<br><sup>21</sup> ,    | NO                                      |
| + LV  | 0  | 2<br>references <sup>22 23</sup> ,                             | NO                                      |

Only the Mayo Clinic regimen--**the labeled regimen**--has consistently demonstrated a survival advantage, in randomized controlled trials, when compared to bolus 5-FU. The Mayo Clinic regimen has demonstrated a survival advantage when compared to bolus 5-FU with two different doses of leucovorin (i.e., 20 mg/m<sup>2</sup> and 200 mg/m<sup>2</sup>). The Mayo Clinic regimen has demonstrated a survival advantage when compared to a sequential MTX→5-FU. The Roswell Park regimen and the prolonged continuous infusion regimens have not demonstrated a survival advantage, in randomized controlled trials, when compared to bolus 5-FU and in the case of the Roswell Park regimen when compared to a sequential MTX→5-FU. In the 1990s, only the Mayo Clinic regimen--**the labeled regimen**--was appropriate as the comparator in noninferiority trials in advanced colorectal cancer with survival as

<sup>4</sup> Journal of Chemotherapy. 1993;5:52-55

<sup>5</sup> Annals of Oncology. 1998; 9:535-541

<sup>6</sup> J Clin Oncol. 1990;8:491-501

<sup>7</sup> Annals of Oncology. 1991;2:673-679

<sup>8</sup> Annals of Oncology. 1992;3:371-376

<sup>9</sup> J Clin Oncol. 1995;13:1303-1311

<sup>10</sup> Dtsch med Wschr. 1992;117:1007-1013

<sup>11</sup> J Clin Oncol 1987;5:1559-65

<sup>12</sup> Proc ASCO 1988;7:97

<sup>13</sup> J Clin Oncol 1989;7:1419-26

<sup>14</sup> Anticancer Res 1992 May-Jun;12(3):607-12

<sup>15</sup> J Clin Oncol. 1993;11:1888-1893

<sup>16</sup> J Clin Oncol. 1995;13:1303-1311

<sup>17</sup> Journal of Clinical Oncology. 1989;7:425-432,

<sup>18</sup> Am J Clin Oncol. 1992;15:518-523

<sup>19</sup> J Clin Oncol. 1995;13:1303-1311

<sup>20</sup> JNCI 1996;88:668-679

<sup>21</sup> Eur J Cancer 1997 Oct;33(11):1789-93

<sup>22</sup> data taken from Rougier in Eur J Cancer 1997 Oct;33(11):1789-93

<sup>23</sup> J Clin Oncol. 1995;13:1303-1311

the primary endpoint. Further clinical research have not demonstrated the safety and effectiveness of the alternative leucovorin/5-fluorouracil treatment regimens.

#### RECOMMENDATION

Further clinical research have not demonstrated the safety and effectiveness of alternative leucovorin/5-fluorouracil treatment regimens (e.g., the Roswell Park regimen and prolonged 5-FU continuous infusion  $\pm$  leucovorin). The paragraph below is outdated and should be deleted from the label (in the DOSAGE AND ADMINISTRATION section, advanced Colorectal Cancer subsection, last paragraph) with the next printing of the label.

"Several other doses and schedules of leucovorin/5-fluorouracil therapy have also been evaluated in patients with advanced colorectal cancer; some of these alternative regimens may also have efficacy in the treatment of this disease. However, further clinical research will be required to confirm the safety and effectiveness of these alternative leucovorin/5-fluorouracil treatment regimens."

ROBERT M. WHITE, JR.  
January 23, 2002

CC:  
NDA #8-107  
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HFD-150/RWHITE  
HFD-150/P GARVEY CSO  
HFD-340  
HFD-150

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