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CRC NCCN Guidelines Panel

On behalf of Acrotech BioPharma LLC, I respectfully request the NCCN Colon Cancer Guideline Panel review the enclosed data and consider for inclusion the sodium-based levoleucovorin, Khapzory™, as a potential alternative to the use of a calcium-based levoleucovorin in conjunction with fluorouracil for treatment of advanced colorectal cancer.

Specific Changes Requested: A footnote in section COL-D-7 stating that the disodium levoleucovorin product Khapzory™ is compatible with fluorouracil (5FU) such that both products may be combined within the same infusion bag, or infused concurrently, in those treatment regimens where the leucovorin-fluorouracil combination is deemed appropriate.

FDA Clearance: Khapzory™ received FDA approval on October 19, 2018 under the 505(b)(2) regulatory pathway for therapeutic equivalents.¹ Khapzory™ is therapeutically identical to other levoleucovorin products but is pharmaceutically differentiated as being the only sodium salt based levoleucovorin (di-sodium levoleucovorin) approved in the United States.

Rationale: In support of this proposed addition, the following provides a comparison of sodium-based levoleucovorin Khapzory™ with the other folate analogs approved in the United States. All other leucovorin or levoleucovorin products currently available in the United States are calcium salt based; calcium- *d,l*-leucovorin or calcium levoleucovorin. Calcium levoleucovorin contains levoleucovorin calcium pentahydrate and mannitol, while Khapzory™ is calcium-free and contains levoleucovorin, sodium hydroxide, and mannitol,¹ resulting in a di-sodium salt formulation.

The addition of folinic acid to fluorouracil has been shown to both enhance the therapeutic effect and increase toxicity of fluorouracil in patients receiving chemotherapy. Many treatment regimens in the current NCCN guidelines for advanced metastatic colorectal cancer include combination therapy with fluorouracil (often in combination with a targeted therapy) in addition to folinic acid as the foundation of the regimen.

Due to calcium content, the labels of calcium-based levoleucovorin and *d,l*-leucovorin include a warning related to the rate of infusion. These products are also incompatible with fluorouracil, requiring sequential administration protocols (leucovorin followed by fluorouracil) in order to avoid calcium carbonate precipitation and potential IV catheter occlusion.² Khapzory™ contains no calcium warning and products in the United Kingdom and Germany containing identical disodium levoleucovorin formulation (Disodium levofolinic acid 50 mg/ml solution for injection or infusion; Levofolinic acid 50mg/ml solution for injection or infusion) have been established as compatible with fluorouracil and may be administered simultaneously with fluorouracil.³

When mixed with or infused simultaneously with fluorouracil, sodium formulations do not pose any catheter occlusion risk, unlike calcium formulations. Clinical studies of disodium levoleucovorin in the treatment of mCRC have demonstrated comparable response rates and toxicity levels with no catheter occlusion, confirming fluorouracil compatibility.^{4,5,6} In the most recent comparative study, a randomized Phase 2 clinical trial variation of the FOLFIRINOX regimen, sequential calcium leucovorin infusion prior to fluorouracil was compared to sodium leucovorin mixed with fluorouracil for simultaneous infusion. This study showed that both sodium leucovorin and calcium leucovorin arms had comparable safety profiles, with response rates for the sodium leucovorin arm being at least as good, if not better, than what was observed with calcium levoleucovorin.⁷


A recent review of preclinical rationale and clinical data comparing results with sequential administration of calcium levoleucovorin followed by fluorouracil, to those for the simultaneous infusion of sodium levoleucovorin with fluorouracil, concluded that these methods appear to have comparable results but with a more favorable efficacy and toxicity profile for a sodium formulation in terms of ORR, mPFS, TTP and the occurrence of severe AEs.⁸

Catheter occlusion may require surgical catheter removal, catheter replacement, admission or re-admission to the hospital, and an increased risk of bacterial infection.⁹ Therefore, if simultaneous administration in combination with fluorouracil is considered, the primary advantage of the sodium-based formulation over a calcium-based formulation may be a more favorable operational profile and improved safety, in addition to enhanced convenience and a cost-saving method of administration.^{6,8}

The following references are submitted in support of this proposed change.

1. Spectrum Pharmaceuticals. *Perscribing Information, Khapzory*. Irvine, Ca : s.n., 2018.
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3. medac GmbH. *Perscribing Information, Levofolinic acid 50 mg/ml solution for injection or infusion*. 2008.
4. Luftner D, et al. Catheter Occlusion by Calcium Carbonate: A Well Known Problem Persists In Spite of Better Knowledge. *Onkologie* 2003;26:425-426.
5. Ardalan, B et al. A Phase II Study of Weekly 24-Hour Infusion With High Dose Fluorouracil With Leucovorin in Colorectal Carcinoma. *J Clin Onc*. 1997;9(4):625-630.
6. Hartung, G et al. Phase II Study of a Weekly 24 Hour Infusion with 5-Fluorouracil and Simultaneous Sodium-Folinic Acid in the First-Line Treatment of Metastatic Colorectal Cancer. *Onkologie* 2001;24(5):457-462.
7. Bleiberg, H et al. A Phase II Randomized Study of Combined Infusional Leucovorin Sodium and 5-FU versus the Leucovorin Calcium Followed by 5-FU Both in Combination with Irinotecan or Oxaliplatin in Patients with Metastatic Colorectal Cancer. *Acta Gastro-Enterologica Belgica* 2012;75:14-21.
8. Ratti, M et al. Major innovations and clinical applications of disodium-levofolinate: a review of available preclinical and clinical data. *Ther Adv Med Oncol* 2019;11:1-10.
9. Ernst, FR et al. Comparison of Hospital Stay, Costs, and Readmission of Alteplase versus Catheter Replacement Among Patients with Occluded Central Venous Catheters. *Journal of Hospital Medicine* 2014;9:490-496.

Sincerely,



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