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NCCN Guidelines Panel: Hematopoietic Growth Factors

On behalf of Pharmacosmos Therapeutics, Inc., I respectfully request the NCCN Hematopoietic Growth Factors Panel review the enclosed data for modification of information as it relates to Monoferic (ferric derisomaltose) in the Management of Cancer- and Chemotherapy-Induced Anemia.

Specific changes:

- Removal of footnote "d" under the table of the "Parenteral Iron Preparations" section ANEM-B as prospective studies evaluating ferric derisomaltose have included patients with cancer- or chemotherapy-induced anemia.
- Change of footnote "e" under the table of the "Parenteral Iron Preparations" section ANEM-B to "Premedications prior to IV iron should not be routinely used unless there is a history of allergy to more than one drug, an allergic diathesis or asthma and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms. If warranted, premedications should be given before any test doses."
- Consider replace "test dose at MD discretion based on risk for reaction" for ferric derisomaltose. for newer IV irons SINCE is only in the label for INFeD, no test dose used in newer irons.

FDA clearance: Ferric derisomaltose is an iron replacement product that is FDA-approved for the treatment of iron deficiency anemia (IDA) in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron.
- who have non-hemodialysis dependent chronic kidney disease (CKD).

Rationale:

In support of the first request to remove footnote "d," the phase 3 FERWON-IDA trial with ferric derisomaltose (or iron isomaltoside as it was previously known) randomized 1512 patients with IDA of mixed etiologies. The study included those with cancer diagnoses, among others like abnormal uterine bleeding, gastrointestinal disease, bariatric procedures. This trial demonstrated that patients treated with a single-dose IV ferric derisomaltose 1000 mg had a significantly more rapid hematological response in the first two weeks, comparable efficacy, more rapid reduction in fatigue, and a similar safety profile compared to repeated doses of iron sucrose (Auerbach, 2019).

Birgegård and colleagues also evaluated the safety and efficacy of ferric derisomaltose compared to oral iron sulfate for the treatment of IDA in patients with chemotherapy-induced anemia. The trial found sustained increases in hemoglobin concentration over time with both products with ferric derisomaltose being better tolerated than oral iron in this patient population (Birgegård, 2016).

In support of the second request to change footnote "e," there is no data to support routine premedication with IV iron products (Cancado, 2011). Premedication was not routinely administered as part of the protocol in the FERWON clinical trials with ferric derisomaltose and the prescribing information does not state that premedications should be given (Auerbach, 2019) (Cancado, 2011) (Pharmacosmos Therapeutics, 2020).

There is published data to show that "the majority of AEs seen when diphenhydramine is prescribed are due to premedication but often attributed to IV iron" (Cancado, 2011). Patients may be put at risk since "antihistamines can cause somnolence, flushing, hypotension and supraventricular tachycardia prompting inappropriate intervention and the conversion of a minor reaction to a serious or life threatening one" (Cancado, 2011). A more recent article notes that "pre-medication with histamine H₁ receptor antagonists has been reported to cause the majority of perceived reactions to IV iron in one large cohort" (Gomez-Ramirez, 2019). Clinicians have recommended the "use of these antihistamines to prevent or treat IV iron infusion reaction be proscribed" (Gomez-Ramirez, 2019).

Cancado and Munoz do recommend premedication only in appropriate cases where "there is a history of allergy to more than one drug, an allergic diathesis or asthma and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms" (Cancado, 2011), hence the requested change to footnote "e."

Regarding the third request to remove the test dose recommendation for ferric derisomaltose, there is no data to support recommending a test dose for ferric derisomaltose and is not a requirement based on the label nor was it studied this way in the pivotal trials (Auerbach, 2019) (Pharmacosmos Therapeutics, 2020). Historically, test doses were required with INFeD and Dexferrum due to their black box warnings, but this is not the case with the newer IV irons (Cancado, 2011). UpToDate and other sources recognize this as well and do not require a test dose with the exception of iron dextran products (UpToDate, 2021)(SABM, 2020).

The following are submitted in support of this proposed change:

1. Auerbach, Michael et al. "A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial." *American Journal of Hematology*, vol. 94,9 (2019): 1007-1014.
2. Birgegård, Gunnar et al. "A Randomized Noninferiority Trial of Intravenous Iron Isomaltoside versus Oral Iron Sulfate in Patients with Nonmyeloid Malignancies and Anemia Receiving Chemotherapy: The PROFOUND Trial." *Pharmacotherapy* vol. 36,4 (2016): 402-14.
3. Cançado, R. D., & Muñoz, M. (2011). Intravenous iron therapy: how far have we come? *Revista brasileira de hematologia e hemoterapia*, 33(6), 461–469. <https://doi.org/10.5581/1516-8484.20110123>
4. Gómez-Ramírez, S., Shander, A., Spahn, D. R., Auerbach, M., Liunbruno, G. M., Vaglio, S., & Muñoz, M. (2019). Prevention and management of acute reactions to intravenous iron in surgical patients. *Blood transfusion = Trasfusione del sangue*, 17(2), 137–145. <https://doi.org/10.2450/2018.0156-18>
5. Monoferric (ferric derisomaltose) [package insert]. Morristown, NJ: Pharmacosmos Therapeutics, Inc.; 2020
6. Intravenous iron products (use in adults). UpToDate. 2021. Accessed 3/3/2021. Available from: https://www.uptodate.com/contents/image?imageKey=HEME%2F106130&topicKey=HEME%2F7148&source=see_link
7. IV Iron Products. SABM. 2020. Accessed 3/3/2021. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwilhb-TwZXvAhXuRd8KHaaQAnoQFjAAegQIARAD&url=https%3A%2F%2Fsabm.org%2Fwp-content%2Fuploads%2F2biii-IV-Iron-Products.pdf&usg=AOvVaw1qV1Ro1JZF48GWzY_Cn3Uf

We greatly appreciate your review of this material. Please do not hesitate to contact me if further information is required.

Kind regards,
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