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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 inclusion of Monoferric (ferric derisomaltose) as a parenteral iron treatment for iron deficiency anemia in the Management of Cancer- and Chemotherapy-Induced Anemia.

Specific changes: Recommend ferric derisomaltose as an intravenous (IV) iron supplementation option by:

- Adding ferric derisomaltose to the ”Recommendations for Administering Parenteral Iron Products” table of the ”Parenteral Iron Preparations” section ANEM-B (i.e.: Name: Ferric Derisomaltose; Test dose: Not recommended; Dosage: 1000 mg IV for patients weighing ≥50 kg or 20 mg/kg actual body weight IV for patients <50 kg; Routes: IV)
- Adding ferric derisomaltose to the ”Intravenous Versus Oral Iron” section (pp. MS-29) of ”Iron Monitoring and Supplementation” in ”Management of Cancer- and Chemotherapy-Induced Anemia”

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: As stated in the current guidelines, ”although oral iron is appropriate for most iron-deficient anemic patients, many patients with chemotherapy-induced anemia either do not respond to oral iron, may be intolerant of oral iron, or may require higher iron doses than achievable with oral iron, making IV iron therapy a valuable option.” Accordingly, the panel currently supports the use of several parenteral iron preparations, including iron sucrose (IS).

One dose of 1000 mg of ferric derisomaltose, which received FDA approval in January 2020, was shown to be non-inferior to up to five doses of IS in increasing hemoglobin levels based on two randomized, actively-controlled and identically designed trials of patients with IDA with intolerance or unsatisfactory response to oral iron (FERWON-IDA and FERWON-NEPHRO)(Auerbach, 2020)(Bhandari, 2020).

The phase 3 FERWON-IDA trial with IDA patients of mixed etiologies (including abnormal uterine bleeding, gastrointestinal disease, bariatric procedures, and cancer) 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 IS (Auerbach, 2020).

The phase 3 FERWON-NEPHRO trial of IDA patients with non-hemodialysis dependent CKD demonstrated that, compared with multiple doses of IS, a single-dose of IV ferric derisomaltose 1000 mg induced a non-inferior 8-week hematological response, comparably low rates of serious or severe hypersensitivity reactions, and a significantly lower incidence of composite cardiovascular adverse events (Bhandari, 2020).

The two studies were powered to show a difference in adjudicated serious or severe hypersensitivity reactions of <3% between ferric derisomaltose and IS treatment groups (non-inferiority criteria). A total of eight patients experienced serious or severe hypersensitivity reactions that were positively adjudicated and assumed related to trial drug; 13 reactions in 6/2008 (0.3%) patients in the ferric derisomaltose group and two reactions in 2/1000 (0.2%) patients in the IS group and thereby ferric derisomaltose demonstrated non-inferiority versus IS. The frequency of hypophosphatemia (serum phosphate <2.0 mg/dL) was low (<4%) in both treatment groups. No patient had a serum phosphate <1 mg/dL. The frequency of adverse drug reactions was similar between treatment groups: 8.6% (172/2008) in the ferric derisomaltose group and 9.0% in the IS group (p=0.681). There were no related fatalities (Bhandari, 2019).

Ferric derisomaltose was studied in two additional trials, the PHOSPHARE trials (IDA4 and IDA5), which were identically designed, prospective, multicenter, open-label, randomized, clinical trials, that evaluated the risks of hypophosphatemia and effects on biomarkers of mineral and bone homeostasis of ferric

derisomaltose vs ferric carboxymaltose (FCM) in 245 patients with IDA. The PHOSPHARE trials demonstrated that the incidence of hypophosphatemia was significantly lower following ferric derisomaltose treatment compared to FCM (trial A: 7.9% in ferric derisomaltose group vs 75.0% in FCM group, P < 0.001; trial B: 8.1% in ferric derisomaltose group vs 73.7% in FCM, P < 0.001)(Wolf, 2020).

Of note, ferric derisomaltose is also known as iron isomaltoside 1000, which is the generic name initially approved in the EU and in some other markets, whereas ferric derisomaltose is the international nonproprietary name (INN) and United States Adopted Name (USAN). Monoferric was first approved outside North America in EU in 2009 as Monofer (iron isomaltoside 1000) and is currently marketed in more than 30 countries worldwide, including in the EU, Canada, and Australia. The publications on FERWON-IDA and FERWON-NEPHRO use the term iron isomaltoside throughout for Monofer/ Monoferric. Additionally, dosing of the product may be different outside of the US (Auerbach, 2020)(Bhandari, 2020).

Studies specifically evaluating the FDA-approved single dose of ferric derisomaltose 1000 mg for the treatment of patients with IDA and cancer have not been performed; however, Birgegård and colleagues evaluated the safety and efficacy of ferric derisomaltose for the treatment of IDA in oncology patients and that data is provided for your review (Birgegård, 2016).

Ferric derisomaltose is contraindicated in patients with a history of serious hypersensitivity to ferric derisomaltose or any of its components. Administration of ferric derisomaltose does not require a test dose (Monoferric PI). The full prescribing information is attached, along with the five articles mentioned.

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. Bhandari, Sunil et al. “Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial.” Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association, gfaa011. 12 Feb. 2020

3. Bhandari, Sunil et al. ”A single 1,000 mg infusion of iron isomaltoside 1000 demonstrates a more rapid hemoglobin response and reduced risk of cardiovascular adverse events compared to multiple doses of iron sucrose in the FERWON trials.” Presented at the 56th ERA-EDTA Congress, Budapest, Hungary, 13–16 June 2019

4. 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.

5. Monoferric (ferric derisomaltose) [package insert]. Morristown, NJ: Pharmacosmos Therapeutics, Inc.; 2020

6. Wolf, Myles et al. “Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials.” *JAMA*, vol. 323,5 (2020): 432-443.

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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