VIEWPOINT

Think Outside the Box With Intravenous Iron—The New Ferric Carboxymaltose FDA Boxed Warning

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On September 1, 2026, the US Food and Drug Administration (FDA) added a boxed warning to ferric carboxymaltose (FCM; Injectafer) to alert health care professionals and patients about the significant risk of hypophosphatemia and its downstream complications, which may lead to severe and potentially life-threatening consequences, including osteomalacia, fractures, cardiac arrhythmias, and neuromuscular dysfunction. The issuance of the boxed warning was in response to a successful FDA Citizen Petition initiated by Cure HHT, the largest international advocacy group for hereditary hemorrhagic telangiectasia. Hypophosphatemia occurs in most adults receiving FCM after a single course of treatment (1-2 doses), often lasts for weeks to months, and may cause serious skeletal complications.[1-3] The granting of this Citizen Petition is a noteworthy triumph of patient advocacy and pharmacovigilance. For context, few FDA Citizen Petitions are granted (even in part) and typically take several years until approval or denial.[4] The time between the filing of this Citizen Petition and its being granted was a remarkable 177 days. Even so, the boxed warning does not go far enough.

In June 2007, the European Medicines Agency first approved the use of FCM, a formulation allowing a complete replacement dose to be administered in a single infusion during 15 minutes. Early enthusiasm was enormous because the initial trials did not reveal the scope, severity, or consequences of FCM-induced hypophosphatemia.[5]

In 2013, Wolf and colleagues[6] reported that iron deficiency itself drove drastic increases in transcription of fibroblast growth factor 23 (FGF23), a normal human phosphaturic hormone. This increase is ordinarily offset by physiologic cleavage of the intact and biologically active hormone, allowing serum phosphate levels to remain normal. It is postulated that FCM-induced hypophosphatemia occurs due to inhibition of degradation of intact FGF23; although the exact mechanism has not yet been elucidated, the hypothesis is that the carboxymaltose moiety is responsible.[7] Moreover, attempts at phosphate repletion increase parathyroid hormone, further worsening hypophosphatemia.[7] Attempts at treatment with calcitriol are also usually ineffective and likely increase the risk of nephrolithiasis.[5,7,8] Insidiously, repeated FCM infusions can gradually demineralize the skeleton, resulting in osteomalacia and pathologic insufficiency fractures.[5,7,8] Diagnosis is hampered because radiographs are insensitive for insufficiency fractures, which are best observed on magnetic resonance imaging or single-photon emission computed tomographic or bone scan. This complication can cause debilitating pain and alarming degradation of musculoskeletal health in younger and older adults alike.[5] Intact FGF23-induced hypophosphatemic osteomalacia is otherwise associated clinically only with a rare genetic disorder (X-linked hypophosphatemic rickets) or a rare paraneoplastic syndrome (tumor-induced osteomalacia), often resulting in missed or incorrect diagnoses. Therefore, it is unsurprising that patients with hereditary hemorrhagic telangiectasia—the second most common inherited bleeding disorder worldwide (1 in 4000 persons) and a disease frequently resulting in lifelong chronic bleeding and recurring intravenous iron treatments—led the charge to get the boxed warning added to the FCM label. This population was effectively ground zero for harms wrought by FCM, which ultimately have affected all populations receiving it, including those with inflammatory bowel disease, abnormal uterine bleeding, and postbariatric surgery.

The evidence base for clinical consequences of FCM-induced hypophosphatemia is well established. A large, prospective, randomized, double-blind trial comparing FCM and ferumoxytol reported equal efficacy but incident hypophosphatemia exceeding 50% in the FCM group (vs <1% in the ferumoxytol group), alongside extreme increases (>300%) in intact FGF23.[3] These data were corroborated in multiple large randomized trials of ferric derisomaltose (FDI) and FCM, reporting similar results, with 50% to 75% of individuals who received FCM developing hypophosphatemia vs less than 8% who received FDI.[1,2] Additionally, approximately 10% of FCM-treated patients (vs none receiving ferumoxytol or FDI) developed severe hypophosphatemia (serum phosphate level <1.0 mg/dL), low enough for severe cardiac, respiratory, muscular, and hemolytic complications. Despite publication of these data, awareness among physicians has been slow to develop and FCM continues to be administered with impunity, often without measurement of phosphorous level preadministration or postadministration. Since FCM's approval in the US in 2013, the number of cases of FCM-induced hypophosphatemia reported to FDA has increased year over year and recently skyrocketed to well over 1000 in total.[5] More than half of these adverse events led to hospitalization, caused disability, were life-threatening, or were fatal. Hypophosphatemia induced by FCM seems almost perfectly designed to avoid routine clinical detection because there is substantial overlap of symptoms of iron deficiency anemia and symptoms of hypophosphatemia (ie, fatigue, decreased exercise, and brain fog), the product effectively treats iron deficiency anemia, and few clinicians actually monitor phosphate levels preadministration and postadministration. Therefore, we have no doubts that the true number of serious cases of FCM-induced hypophosphatemia far exceeds those reported to FDA. Despite the reports, compounding evidence for harm, and FCM's high financial cost, it remains the market leader, with a market share of nearly 50%.

As if the significant and repeated findings of acute, protracted, and potentially severe hypophosphatemia from large randomized trials were insufficient to inform on action, a recent landmark study on FCM-induced complications reported statistically significantly higher risk of fractures, osteomalacia, and nephrolithiasis in recipients of FCM compared with FDI.[8] In addition to analysis of a large

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clinical cohort, the authors reported deranged bone mineral metabolism in a mouse model by comparing the effects of low-molecular-weight iron dextran, FDI, and FCM in a murine preosteoblast cell line that modeled osteogenic differentiation and extracellular matrix formation. Compared with the other iron formulations, FCM caused osteoblasts exposed to it to exhibit higher intracellular iron deposition, and only FCM resulted in reduced bone extracellular collagen deposition. These and other data suggest detrimental effects of FCM on bone extend beyond hypophosphatemia and its complications; FCM itself may be osteotoxic independent of effects on phosphate metabolism.

Despite the extensive postapproval clinical trial data, new boxed warning, and mandated phosphate monitoring, the FDA label for FCM still inexplicably lists the incidence of hypophosphatemia as 2%. To the label's credit, it does include the 33% incidence in the pediatric trial leading to approval in children, yet this does not appear to have affected its pediatric use. Ferric carboxymaltose is the only intravenous iron capable of rapid single-dose iron replacement that is FDA approved for children, resulting in preferential formulary placement in many pediatric hospitals nationwide. Widespread pediatric FCM use raises major concerns regarding the potential effect of FCM-induced hypophosphatemia on the growing and developing skeleton, particularly with repeated treatments. To our knowledge, no studies have investigated this question.

Ultimately, for patients, physicians, and regulatory agencies, the final calculus is one of risk vs benefit. Intravenous iron is essential for many patient populations. Were FCM the only available intravenous iron product, the risk-to-benefit calculus may be different. But the 5 other intravenous iron formulations available in the US have trivial to minimal risk of hypophosphatemia or its complications, and 3 of them allow the same complete replacement dosing (on or off label) in a brief single visit. Most of these formulations are considerably less expensive than FCM. The new FDA boxed warning is a step in the right direction. However, given the alternatives, along with the overwhelming clinical and scientific evidence of the metabolic, kidney, and skeletal risks of FCM, we believe the risks of this agent clearly outweigh its benefits. We hope that regulatory agencies will eventually agree.

ARTICLE INFORMATION

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