PHARMANOTE®

Vol. 36, Issue 3 December 2020 Established 1985

Accrufer® (ferric maltol): A Novel Oral Iron Replacement Product for the Treatment of Iron Deficiency in Adults

Michael Vincent, PharmD Candidate

Iron is an essential element in humans and plays a key role in numerous metabolic processes, including oxygen transport, DNA synthesis, and electron transport.[1] Iron deficiency (ID) is the most common and widespread nutritional disorder in the world, with anemia due to iron deficiency affecting a staggering two billion people - approximately more than 30% of the world's population.[2] Groups that are at a high risk of experiencing iron deficiency are those who have inadequate access to iron rich foods during stages of increased iron demand, such as pregnant women, women of childbearing age with heavy menstrual flow, adolescents, and preschool children, with those in developed countries predominantly affected by iron deficiency.[2] In clinical practice, iron deficiency is also a common complication of several chronic medical conditions, including cancers (42.6% across different tumors), inflammatory bowel disease (IBD) (45%), chronic kidney disease (CKD) (24-85%), chronic heart failure (CHF) (43-100%), and other chronic inflammatory diseases.[3-7]

Iron deficiency results from the reduction or even depletion of iron stores over an extended period of time when iron absorption cannot keep up with meeting metabolic demands for iron and replenishing losses of iron.[8] Primary causes of iron deficiency include impaired iron absorption, low intake of bioavailable iron, increased iron requirements, pregnancy, menstruation, and excessive blood loss.[9,10]

Although iron deficiency can occur without anemia and result in some functional impairments, the majority of functional deficits are accompanied by the development of anemia.[8] Iron deficiency anemia (IDA) symptoms include tachycardia, tachypnea, hypotension, fatigue, weakness, headache, cold sensitivity, reduced cognitive function, depression, and decreased work performance.[11-15]

Laboratory diagnosis of iron deficiency itself is straightforward in most individuals (serum ferritin <30 ng/mL), except in certain clinical situations, including inflammatory disorders, infections, and CKD where guidelines developed by professional associations for each specialty should be consulted for diagnosis and treatment of iron deficiency.[16-20] When considering the diagnosis of ID in the presence of other diseases, such as genetic or inflammatory conditions, it is important to consider the entire clinical picture and other iron indices, rather than relying on serum ferritin alone, because these values can be altered.[18,20,21]

In patients with iron deficiency without anemia, the first treatment step in all cases is to asses and address the possible underlying cause of iron deficiency, and whenever possible, eliminate or correct the etiological cause of ID.[21] Once absolute iron deficiency is confirmed, oral iron supplementation as the mainstay of therapy, per the American Society of Hematology Guidelines on Management of Iron Deficiency, for a majority of stable patients (i.e. absence of severe anemia (Hb <7-8 g/dL), chronic blood loss, and dialysis-dependent CKD being treated with erythropoiesis-stimulating agents) who do not require intravenous iron supplementation.[21] Oral iron preparations currently on the market such as ferrous sulfate, ferrous gluconate, and ferrous fumarate appear to be equally efficacious, however they have a high propensity for causing gastrointestinal intolerance.[22-25] For patients intolerant or unresponsive to oral iron therapy, intravenous iron formulations (i.e. iron dextran, iron sucrose, ferric carboxymaltose) are second-line alternatives.[21,26] While effective at normalizing hemoglobin levels and replenishing iron stores, IV iron supplementation comes with high healthcare costs, inconvenience of intravenous infusion in a healthcare facility, risks of hypersensitivity reactions, and possibly serious treatment-related adverse effects that must be considered when making treatment decisions.[21,26]

Accrufer® (ferric maltol) is an oral non-salt-based iron formulation that has received approval from the U.S. Food and Drug Administration (FDA) in July 2019 for the treatment of iron deficiency in those 18 years of age or older with or without anemia.[27,28] This innovative ferric iron-maltol complex has been shown to be less toxic to the gastrointestinal tract mucosa as opposed to currently available oral iron therapies, which are formulated as iron salts composed of ferrous (Fe2+) iron.[24,29-31] This medication offers a unique and convenient treatment alternative to treat iron deficiency in patients who are intolerant to oral iron salt therapies. The purpose of this article is to assess the safety and efficacy of ferric maltol for the treatment of iron deficiency in

IN THIS ISSUE

adults.

Pharmacology

Chemistry and Mechanism of Action

Ferric maltol is an oral non-salt-based iron formulation composed of iron in a stable ferric (Fe3+) state as a complex with a trimaltol ligand, a naturally occurring sugar derivative.[27,29] After oral administration, ferric iron is delivered to the intestinal wall as a biologically labile complex.[32,33] Upon intestinal uptake via enterocytes in the small intestine, this complex dissociates, and iron is taken up across the intestinal wall and transferred to transferrin, the iron transport protein, then subsequently to ferritin, the iron storage protein in systemic circulation.[27,32,33]

The maltol ligand in FM remains complexed to ferric iron until intestinal uptake, thus minimizing the formation of free iron in the gastrointestinal tract, and allowing more efficient uptake of elemental iron into enterocytes, unlike oral therapies containing ferrous iron salts.[32,33] Through more efficient iron delivery and uptake, this allows ferric maltol to be effectively administered at relatively lower daily elemental iron doses as compared to current oral iron formulations.[32-34] Furthermore, unlike unabsorbed ferrous iron, any ferric iron that is not absorbed, remains in a chelated form, as opposed to ferrous iron salts, which can undergo oxidation in the gastrointestinal tract and lead to the subsequent generation of reactive oxygen species (ROS) which causes a wide array of gastrointestinal adverse effects.[34,35]

Pharmacokinetics

Ferric maltol dissociates upon uptake from the gastrointestinal tract, allowing iron and maltol to be absorbed and metabolized independently.[27,32,33] Following a single dose and after one week of multiple doses (at steady state) of FM 30 mg, 60 mg, or 90 mg twice daily (1 one to three times the approved recommended dosage, respectively) maximum serum iron concentrations and transferrin saturation (TSAT) values were both reached by two to three hours after the first dose of FM on day one in all groups.[36] The peak mean serum iron concentration and TSAT value in the FDA approved FM 30 mg twice daily group were 32.3 µmol/L and 45.6%, respectively. Both serum iron concentrations and TSAT values increased in all groups, with higher values achieved in the groups receiving higher doses of ferric maltol. These iron parameters did not exhibit a linear relationship with higher doses. Both total serum iron concentration and TSAT were comparable between day one and day eight exposure with key constituents of FM showing predictable pharmacokinetics and no accumulation over the study period. There was no clear relationship between either iron parameter profile and maltol or maltol metabolite exposure. Mean serum ferritin concentrations increased in all three treatment groups, with notably higher values recorded on day eight as compared with day one, and with greater ferritin levels seen in the groups treated with higher doses of ferric maltol.

Upon absorption from the gastrointestinal tract, maltol is rapidly metabolized to maltol glucuronide through sulfation and glucuronidation via UGT1A6 in vitro.[27] Plasma concentrations of both maltol and maltol glucuronide, reached maximum plasma concentrations in 1–1.5 h before declining to baseline levels within six hours.[36] Maltol and maltol glucuronide showed comparable dose-dependent pharmacokinetic profiles between day one and day eight, indicating insignificant accumulation after twice daily dosing of ferric maltol. Maltol was rapidly excreted in the urine with 40-60% excreted as maltol glucuronide and less than 0.01% excreted as unchanged maltol. Of note, food has been shown to decrease the bioavailability of iron after administration of ferric maltol.[27]

Table 1 | Select Ferric Maltol Pharmacokinetics[27,36]

Absorption	
C_{max}[a] (Serum Iron)	32.3-49.1 µmol/L
T_{max}[b] (Serum Iron)	2-3 hours
C_{max} (TSAT[c])	45.6-69.8%
T_{max} (TSAT)	1-1.5 hours
Metabolism	
Rapid metabolism of maltol to maltol glucuronide	
Elimination	
$T_{1/2}$[d] (Maltol)	0.48-1.17 hours
Urinary Excretion	40-60% as maltol glucuronide <0.01% unchanged

[a]Maximum concentration; [b]Time to maximum plasma concentration; [c]Transferrin saturation; [d]Half-life

Clinical Trials

The FDA approval of Accrufer® (ferric maltol) was based on three placebo-controlled phase III trials: AEGIS-1, AEGIS-2, and AEGIS-CKD clinical trials.[24,27,37] In addition, the FDA reviewed data from the open-label extension (OLE) phase of AEGIS-1 and AEGIS-2 to evaluate the long-term safety and efficacy of continued ferric maltol use.[25] There was also an active comparator phase 3b trial, AEGIS-H2H, published in abstract form with preliminary data, that was not included in the FDA approval, but is reviewed below.[38]

AEGIS-1 and AEGIS-2

Gasche et al. conducted a phase III clinical trial program comprised of two identical clinical trials that evaluated IBD patients with IDA in a 12-week, randomized, double-blind, placebo-controlled, multicenter clinical trial that took place across centers in Austria, Germany, Hungary, and the United Kingdom.[24] Both trials followed the same study design and protocol, with the exception that AEGIS-1 enrolled patients with ulcerative colitis (UC), while AEGIS-2 enrolled patients with Chron's disease (CD). The results from AEGIS-1 and AEGIS-2 were combined into a single data set and analyzed. All patients 18 years or older were required to be in remission or to have a mild-to-moderate disease activity of either UC (defined as a Simple Clinical Colitis Activity Index [SCCAI] score less than four at screening and randomization) or CD (defined as a Crohn's Disease Activity Index [CDAI] score of less than 220 at randomization). Patients included had mild-to-moderate IDA, defined as a Hb concentration ≥9.5 and <12.0 g/dL for females and ≥9.5 and <13.0 g/dL for males and serum ferritin levels <30 µg/L at screening.[39] Patients were also required to have previously failed on treatment with oral ferrous products (OFP) for one or more of the following reasons: 1) adverse drug effects (at least one: nausea, diarrhea, constipation, abdominal pain, flatulence) that led to discontinuation of OFP; 2) deterioration of the primary disease caused by OFP; 3) lack of efficacy; and 4) other signs of OFP failure (or documented reasons why OFP could not be used). Patients were excluded if

Table 2 | Summary of Primary Endpoint Results in Ferric Maltol Phase III Clinical Trials

Trial	Primary Outcome	Intervention (n)	Results	Treatment Difference[a] (CI) [b/c]	P-value
AEGIS-1 and AEGIS-2[24]	Change in Hb[d] from baseline to week 12, LSM[e] (SE[f]) g/dL	FM[g] 30 mg bid (n=64)	2.25 (0.12)	2.18 (1.81)[b]	<0.0001
		Placebo (n=64)	0.06 (0.13)		
AEGIS-1 and AEGIS-2-OLE[25]	Change in Hb from baseline to week 64. mean (SD[h]) g/dL	Continued[i] (n=50)	3.07 (1.46)	-	-
		Switch[j] (n=47)	2.19 (1.61)		
AEGIS-CKD[37]	Change in Hb from baseline to week 16, LSM (SE) g/dL	FM 30 mg bid (n=111)	0.50 (0.12)	0.52 (0.10 to 0.93)[c]	0.0149
		Placebo (n=56)	-0.02 (0.17)		

Trial	Primary Outcome	Intervention (n)	Results	Risk Difference (95% CI)	P-value
AEGIS-H2H[38]	Responder Rate[k], % (PP[l])	FM 30 mg bid (n=78)	67.9	-0.17 (-0.30 to -0.05)	0.341
		IV FCM[m] (n=88)	85.2		
	Responder Rate, % (ITT[n])	FM 30 mg bid (n=125)	67.2	-0.17 (-0.28 to -0.06)	0.298
		IV FCM (n=125)	84.0		

[a]Refers to the least squares mean difference between ferric maltol versus placebo for the primary outcome measure; [b]Confidence interval—refers to a one sided lower 97.5% confidence interval; [c]Confidence interval—refers to a 95% confidence interval; [d]Hemoglobin; [e]Least squares mean; [f]Standard error; [g]Ferric Maltol; [h]Standard deviation; [i]refers to participants initially randomized to the FM treatment arm in the AEGIS-1 and AEGIS-2 trials and who continued FM in the OLE; [j]refers to participants initially randomized to the placebo treatment arm in the AEGIS-1 and AEGIS-2 trials and who switched to FM in the OLE; [k]defined as achieving either a ≥2 g/dL increase in Hb from baseline or Hb normalization (i.e. females: >12 g/dL; males: >13 g/dL)[39] at week 12; [l]Per protocol analysis; [m]Ferric carboxymaltose; [n]Intention to treat analysis

they had anemia unrelated to iron deficiency or if they had received depot iron preparations, erythropoietin, or blood transfusions within 12 weeks of screening. Other reasons for exclusion were receiving oral iron treatment within four weeks of randomization; treatment with immunosuppressants known to induce anemia (e.g. methotrexate, cyclosporin, tacrolimus); dose changes of immunosuppressive or immunomodulatory therapy <4 weeks before randomization; folate deficiency; uncorrected vitamin B-12 deficiency; serum creatinine >2.0 mg/dL; abnormal liver function tests; and pregnancy.

Participants were randomized in a 1:1 ratio to receive either oral ferric maltol or placebo. Participants received either ferric maltol 231.5 mg (equivalent to 30 mg of elemental iron), to be taken orally with water on an empty stomach first thing in the morning before breakfast and last thing at night (twice a day dosing), or matched placebo capsules that were administered similarly.

The primary efficacy endpoint was change in Hb concentration from baseline to week 12. Relevant secondary efficacy endpoints included changes in Hb concentration from baseline to weeks 4 and 8, serum ferritin concentration changes from baseline to week 12, and percentage transferrin saturation (TSAT) changes from baseline to week 12. Both primary and secondary efficacy evaluations were based on an intention-to-treat (ITT) analysis of all randomized patients who had received at least one dose of study medication (ITT full analysis set [FAS]). A responder analysis was also conducted, where responders to treatment were defined as participants who achieved increases in Hb of ≥1 g/dL or ≥2 g/dL, or Hb normalization by week 12 (defined as Hb values ≥12 g/dL for females or ≥13 g/dL for males39). Safety and tolerability were assessed based on adverse events (AEs), vital sign measurements, and routine hematological and blood chemistry indices. Adverse effects were deemed to be treatment-related if there was a reasonable possibility that the AE may have been caused by the study drug based on investigator opinion.

Of the 329 patients screened, 128 were randomized to treatment (FAS). The per-protocol (PP) population was comprised of 104 patients, with 55 FM-treated patients and 53 placebo-treated patients completing the 12 weeks of study therapy. Baseline demographics and disease characteristics were generally comparable between treatment groups. Reasons for previous OFP failure were most commonly GI adverse effects and lack of efficacy in approximately 69% and 37% of participants, respectively. Baseline mean laboratory values for Hb, ferritin, and TSAT as well as relevant concomitant immunosuppressive or immunomodulatory medications are similar between the two treatment groups.

In the primary efficacy analysis, the mean improvement in Hb concentration from baseline to week 12 in the FM group vs placebo was 2.25 g/dL ($P < 0.0001$ based on ANCOVA). In the FM group, absolute mean Hb concentrations improved from

11.00 (SD 1.03) g/dL at baseline to 13.20 g/dL (SD 1.04) with the placebo group remaining unchanged at 11.10 g/dL (SD 0.85) and 11.20 g/dL (SD 0.98).

In the responder analysis, a majority of FM-treated patients achieved ≥1 g/dL and ≥2 g/dL increases in Hb concentration or normalization with 66% of patients treated with FM achieve normalization of Hb concentrations (Hb values ≥12 g/dL for females or ≥13 g/dL for males39) versus 13% of placebo-treated patients (OR = 15.3; 95% CI = 5.9-39.3). Among evaluable FM-treated participants (n=64), the median time to Hb normalization was 57 days. Iron indices, which encompassed serum ferritin and TSAT, improved in the FM-treated group from baseline to week 12, yet remained comparatively unchanged in the placebo group.

During the 12-week study period, treatment-emergent adverse effects (TEAEs), which were largely gastrointestinal in nature and of mild or moderate severity, were documented in 58% of FM-treated participants and 72% of participants in the placebo group. Upon investigator review, AEs were characterized as related to study medication (FM vs placebo) in 25% of FM-treated participants as compared to 11.7% of placebo participants, with the most commonly reported treatment-related AEs (TRAEs) being abdominal pain, constipation, and flatulence. Premature discontinuation due to AEs occurred in 8 (13%) participants in the FM group and 5 (8%) participants in the placebo group, with all treatment-related AEs that led to discontinuation of treatment being gastrointestinal in nature. No serious AEs occurred that were considered to be study medication related.

AEGIS-1 and AEGIS-2 – OLE

Schmidt et al. conducted a 52-week open-label extension (OLE) phase of the aforementioned AEGIS-1 and AEGIS-2 clinical trials to evaluate the long-term efficacy and safety of continued FM treatment in IBD patients with IDA.[25] The OLE phase included participants from the AEGIS-1 and AEGIS-2 clinical trials and utilized the same inclusion and exclusion criteria.[24] During randomized treatment in AEGIS-1 and AEGIS-2, participants received either FM 30 mg or matching placebo orally twice daily for 12 weeks.[24] After week 12, all participating patients in the FM group continued with their ongoing treatment for an additional 52 weeks (total FM treatment period: 64 weeks). Participants who received placebo from weeks 1–12 were switched to receive treatment with FM 30 mg orally twice daily between week 13 and week 64 (total FM treatment period: 52 weeks).

The primary efficacy endpoint was the absolute change in hemoglobin from baseline, where baseline was day zero of treatment, with either FM or placebo at the beginning of randomized therapy. The proportion of patients achieving normalization of hemoglobin levels (Hb values ≥12 g/dL for females or ≥13 g/dL for males39) by week 64 was also assessed. In addition, absolute serum ferritin concentration and TSAT were measured at 4- to 12 - week intervals. All efficacy endpoints were evaluated based on an ITT FAS, as defined in the previous trials. Safety and tolerability were assessed similarly to previous trials.

A total of 97 patients entered the 52-week OLE study phase with 50 from the FM-treatment group ("continued" group) and 47 from the placebo ("switch" group). A total of 37 "continued" and 36 "switch" participants completed the 52 weeks.

Absolute mean hemoglobin concentrations increased from a baseline of 11.00 (SD 1.03) g/dL to 13.95 (SD 1.26) g/dL at week 64 in the "continued" group. In the "switch" group, absolute mean hemoglobin concentrations increased from 11.10 (SD 0.85) g/dL at baseline to 13.33 (SD 1.46) g/dL at week 64. In both treatment groups, the greatest increases in hemoglobin concentration occurred during the initial 12 weeks of treatment with FM with increases similar among both treatment groups. Beyond the initial 12 weeks of FM-treatment, hemoglobin concentrations were maintained for the remainder of the study period with hemoglobin normalization achieved in 86% of participants at week 64 ("continued" group: 89% vs "switch" group: 83%). Iron indices, which included serum ferritin and TSAT measurements, showed a pronounced degree of variability overall among study participants. This led to no statistically significant differences in iron parameters, despite observed improvements in both serum ferritin and TSAT during open-label FM treatment.

During the study period, 80% of the participants reported at least one TEAE, which were primarily gastrointestinal in nature. However, only 24% of FM-treated participants experienced AEs deemed related to therapy. These TRAEs were similar to aforementioned trials and are summarized in the Adverse Effects and Precautions section. Premature discontinuation of FM treatment due to AEs during the entire 64-week study period occurred In a total of 18 (16%) participants, with 12 (11%) participants discontinuing FM treatment during the extension period. Ten discontinuations were judged to be related to the natural course of the patients' disease and not the study medication.

AEGIS-CKD

Kopyt et al. conducted a 16-week phase III, randomized, double-blind, placebo-controlled, prospective, multicenter clinical trial known as the AEGIS-CKD study, which evaluated the efficacy and safety of ferric maltol for the treatment of IDA in patients with non-dialysis dependent chronic kidney disease (NDD-CKD).[37] This study included patients 18 years or older with a current clinical diagnosis of CKD with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and ≥15 mL/min/1.73 m^2 as calculated using the abbreviated version of the Modified Diet in Renal Disease (MDRD) equation. All patients were required to have IDA, defined as a Hb concentration <11.0 g/dL and ≥8.0 g/dL, and either serum ferritin <250 µg/L with TSAT <25% or serum ferritin <500 µg/L with TSAT <15%. Notable exclusion criteria include if patients were currently receiving dialysis, if initiation of dialysis was considered likely during the study period, or renal transplantation in the previous 12 months. Other exclusion criteria was similar to previous trials. All efficacy endpoints were evaluated based on an ITT analysis, as defined in the previous trials. Safety and tolerability were assessed similarly to previous trials.

Participants were randomized in a 2:1 ratio to receive either FM 30 mg orally twice daily or matching placebo capsules orally twice daily for 16 weeks. Of the 167 patients enrolled, 111 received FM and 56 received a matching placebo control. Baseline demographics and disease characteristics were similar between the two treatment groups with a mean age of approximately 67 years-old with mean hemoglobin concentrations (FM group: 10.06 (SD 0.77) g/dL vs placebo group: 10.03 (SD 0.82) g/dL). The mean eGFR (FM group: 31.9 mL/min/1.73 m^2 vs placebo group: 29.7 mL/min/1.73 m^2) were also similar between both groups.

The primary endpoint was change in Hb concentration from baseline to week 16 which was found to be superior in the FM group 0.5 (SD 0.122) g/dL vs placebo group -0.02 (SD 0.165) g/dL (treatment difference of 0.52 (SD 0.210) g/dL (95% CI [0.102-0.930]; P = 0.0149).

In the secondary efficacy analyses, relevant endpoints included a statistically significant percentage of FM-treated participants

achieved a Hb concentration ≥11 g/dL by week 16 as compared the placebo group (FM group: 26% vs placebo group: 17.5%) (OR = 2.60; 95% CI [1.20-6.60]; P = 0.0442). In addition, there was a statistically significant improvement observed in all iron parameters (serum ferritin, TSAT, and serum iron) from baseline to week 16 in the FM group vs placebo group.

During the study period, 68% of patients reported at least one TEAE which were primarily gastrointestinal in nature with 19% thought to be related to therapy. These TRAEs were similar to aforementioned trials and are summarized in the Adverse Effects and Precautions section. A higher proportion of participants treated with FM completed the 16 weeks of treatment as compared to placebo-treated participants (FM group: 81% vs placebo group: 70%). Premature discontinuation of FM-treatment due to TEAEs during the 16-week study period, occurred in 7 (6.3%) participants, with 2 (2%) participants discontinuing FM-treatment due to TEAEs that were deemed to be related to the study drug. The data specifying the description of these TEAEs are currently unavailable.

At the time of this writing, results of this study have only been published in abstract format.

AEGIS-H2H

Howaldt et al. conducted a phase 3b, randomized, controlled, open-label, prospective, multicenter head-to-head active-comparator non-inferiority clinical trial known as the AEGIS-H2H study, which evaluated the efficacy and safety of ferric maltol and intravenous ferric carboxymaltose (IV FCM) in the treatment of IDA in patients with IBD.[38] This study included patients ages 18 years and older with a clinically confirmed diagnosis of IBD. All patients were required to have IDA, defined as Hb concentration ≤11.0 g/dL and >8.0 g/dL for women or Hb concentration ≤12.0 g/dL and >8.0 g/dL for men, and either serum ferritin <30 ng/mL or serum ferritin <100 ng/mL with TSAT <20%. All patients must have been considered suitable for IV iron treatment by the investigator to be eligible for study enrollment. Exclusion criteria was similar to previous trials. The study period for this trial was 52 weeks of randomized treatment with either FM or IV FCM. Primary and secondary endpoints were evaluated after the first 12 weeks. Long-term efficacy and safety endpoint evaluations occurred at week 52.

Participants were randomized in a 1:1 ratio to receive either FM 30 mg orally twice daily or IV FCM administered according to local prescribing information for 52 weeks. For participants in the IV FCM treatment group, IV iron treatment was repeated if the participant was iron deficient at any of the follow-up visits during the study period.

The primary efficacy endpoint was Hb response rate at week 12, defined as the proportion of patients achieving either a ≥2 g/dL increase in Hb from baseline or normalization of Hb (i.e. females: >12 g/dL; males: >13 g/dL39). Both PP and ITT populations were utilized in assessing non-inferiority of the primary efficacy endpoint. The pre-defined non-inferiority margin for risk difference in response rate at week 12 was set at less than 20% for both the PP and ITT populations.

Secondary efficacy endpoints included change in Hb concen-

Table 3 | Summary of Select Secondary Endpoint Results in Ferric Maltol Phase III Clinical Trials

Trial	Secondary Outcome	Intervention (n)	Results	Treatment Difference	P-value
AEGIS-1 and AEGIS-2[24]	Change in serum ferritin from baseline to week 12, mean µg/L	FM[b] 30 mg bid (n=64)	17.4 vs 1.6	ETD[c] 15.8	-
	Change in TSAT[a] from baseline to week 12, mean %	Placebo (n=64)	17.9 vs 0.3	ETD 17.6	-
AEGIS-1 and AEGIS-2-OLE[25]	Hb[d] normalization[e] at week 64, %	Combined[f] (n=97)	86	-	-
	Change in serum ferritin from baseline to week 64, mean µg/L		49.0	-	-
	Change in TSAT from baseline to week 64, mean %		18.5	-	-
AEGIS-CKD[37]	Hb ≥11 g/dL at week 16, %	FM 30 mg bid (n=111)	26.0 vs 17.5	OR[h] 2.60 (95% CI 1.02 to 6.60)	0.0442
	Change in serum ferritin from baseline to week 16, LSM[g] µg/L		25.49 vs –8.25	ETD 33.7 (95% CI 15.3 to 52.2)	0.0004
	Change in TSAT from baseline to week 16, LSM %	Placebo (n=56)	3.78 vs –0.69	ETD 4.47 (95% CI 2.29 to 6.65)	<0.0001
AEGIS-H2H[38]	Hb normalization at week 4, %	FM 30 mg bid (ITT[i]; n=125)	24.8 vs 48.0	ETD -23.2	-
	Hb normalization At week 12, %		55.2 vs 80.8	ETD -25.6	-
	≥2 g/dL increase in Hb at week 4, %	IV FCM[j] (ITT; n=125)	20.8 vs 60.0	ETD -39.2	-
	≥2 g/dL increase in Hb at week 12, %		60.8 vs 76.8	ETD -16.0	-

[a]Transferrin saturation; [b]Ferric maltol; [c]Estimated treatment difference; [d]Hemoglobin; [e]Defined as female >12 g/dL and males >13 g/dL; [f]Includes all patients treated with ferric maltol in the OLE study phase (i.e. "continued" and "switch" treatment groups); [g]Least squares mean; [h]Odds ratio; [i]Intention to treat analysis; [j]Ferric carboxymaltose

tration from baseline to week 12, the proportion of participants who experienced a change of ≥1.0 g/dL or ≥2.0 g/dL in Hb concentration from baseline to week 12, and the proportion of participants with Hb concentrations within normal limits (i.e. females: >12 g/dL; males: >13 g/dL39) at week 12. These secondary outcomes were also assessed at week 4. There were additional secondary efficacy endpoints evaluating the same aforementioned outcome measures specifically in participants with a baseline Hb <9.5 g/dL. Relevant long-term efficacy endpoints included the proportion of participants who were non-anemic at 6 and 12 months, the proportion of participants who achieved normalization of ferritin levels at 6 and 12 months.

Of the 462 patients screened, 250 were randomized to treatment, with 125 patients in each treatment group. A total of 93 FM -treated patients and 106 IV FCM-treated patients completed the 52-week study period. The PP population was comprised of 166 patients (FM group: n=78 vs IV FCM group: n=88). Baseline demographics and disease characteristics were generally comparable between the two treatment groups with a mean age of approximately 40-years-old and a similar proportion of patients with UC and CD between both groups (UC: 38.5% and CD: 61.5%). Hemoglobin concentrations <9.5 g/dL (FM group: 24.4% vs IV FCM group: 30.1%) and ≥9.5 g/dL (FM group: 75.6% vs IV FCM group: 69.9%) were generally comparable between the treatment groups at baseline.

Hemoglobin response rate at 12 weeks, the primary efficacy endpoint, was achieved in 67.9% of FM-treated participants and 85.2% of IV FCM-treated patients in the PP population (RD -0.17; 95% CI [-0.30 to -0.05]; P = 0.341). For the ITT population, 67.2% of FM-treated patients and 84.0% of IV FCM-treated patients displayed Hb response (RD -0.17; 95% CI [-0.28 to -0.06]; P = 0.298). Non-inferiority was not achieved at 12 weeks in the primary endpoint for either the PP or ITT population.

In the secondary efficacy analyses, IV FCM-treated participants displayed a greater mean change in Hb concentration from baseline to week 4 (FM group: 1.27 (SD 0.974) g/dL vs IV FCM group: 2.19 (SD 1.133) g/dL) and week 12 (FM group: 2.45 (SD 1.449) g/dL vs IV FCM group: 3.04 (SD 1.576) g/dL) as compared to FM-treated participants. The proportion of participants who achieved normalization of Hb concentration at week 4 (FM group: 24.8% vs IV FCM group: 48.0%) and week 12 (FM group: 55.2% vs IV FCM group: 80.8%) was larger in the IV FCM group as compared to the FM group. In patients with a baseline Hb concentration <9.5 g/dL, IV FCM demonstrated greater mean improvements in Hb concentrations and Hb normalization at week 4 and week 12 in comparison to ferric maltol. For long-term efficacy endpoints, FM and IV FCM demonstrated generally comparable effectiveness at maintaining Hb and iron status for up to 52 weeks.

Over the course of the 52-week study period, 75 of 127 participants (59.1%) in the FM group and 43 of 120 participants (35.8%) in the IV FCM group experienced nonserious TEAEs. Among participants treated with FM, gastrointestinal disorders were the most commonly experienced AEs and were similar to those seen in previous studies, which occurred in 40 of 127 participants (31.5%). In comparison, the most commonly experienced AEs in the IV FCM group were infections and infestations (i.e. nasopharyngitis, upper respiratory tract infection, and urinary tract infection), which occurred in 22 of 120 participants (18.3%). In the FM group, 12 of 127 participants (9.4%) and 3 of 120 participants (2.5%) in the IV FCM group experienced serious adverse effects. The data specifying the description of these serious TEAEs and whether they led to premature discontinuation are currently unavailable. At the time of this writing, results of this study have only been published in abstract format.

Adverse Effects and Precautions

The most common adverse events reported in clinical trials were flatulence (4.6%), diarrhea (4%), constipation (4%), discolored feces (4%), abdominal pain (2.9%), nausea (1.7%), vomiting (1.7%), abdominal discomfort (1.1%), and abdominal distension (1.1%).27 During double-blind placebo-controlled trials, the proportion of patients taking FM who discontinued treatment due to adverse reactions was 4.6%, with the most common adverse reaction leading to discontinuation being abdominal pain.[24,27,37]

The FDA-approved labeling recommends avoiding using FM in patients experiencing an active IBD flare because of a potentially increased risk of inflammation in the gastrointestinal tract.[27] As with other iron products, there is a potential for iron overload with excessive therapy, so it is recommended to avoid administration of FM in patients with evidence of iron overload or those currently receiving IV iron products.[27]

Ferric maltol is contraindicated in patients with a history of hypersensitivity reactions to FM, hemochromatosis and other iron overload syndromes, or those receiving repeated blood transfusions.[27]

Drug Interactions

To date, no controlled clinical studies have been conducted which evaluate the drug interaction potential of FM. Currently available information on drug interactions is based upon published case reports and clinical studies that could not be confirmed by controlled studies with FM.[27] Concomitant use of iron products with dimercaprol is recommended to be avoided due to an increased risk of nephrotoxicity. For oral drugs that may reduce the bioavailability of iron it is recommended to separate the administration of FM by at least four hours from these medications.[27]

Dosage and administration

The recommended dosage of FM is 30 mg by mouth twice daily on an empty stomach, taken 1 hour before or 2 hours after a meal.[27] Do not open, break, or chew FM capsules. The available dosage form includes 30 mg capsules with 30 mg of elemental iron and 201.5 mg of maltol.[27]

There appears to be no clinically meaningful change in maltol or maltol glucuronide exposure in non-dialysis dependent CKD (eGFR of >15 mL/min/1.73m^2 and <60 mL/min/1.73m^2) patients, thus there are no renal dose adjustments recommended for patients with renal impairment.[27]

Treatment duration is generally at least 12 weeks, but should be individualized to the patient, as it will largely depend on the severity of their iron deficiency.[21,27] It is recommended that treatment should be continued for as long as necessary until ferritin levels are within normal range.[27]

Cost and Availability

Accrufer® (ferric maltol) is not yet commercially available in the USA. Currently, Shield Therapeutics is in the process of choosing a commercial partner to market Accrufer® (ferric maltol) in the

USA.[28] To date, the CEO of Shield Therapeutics and the company itself has yet to publicly comment on the expected pricing of this medication. Thus, the medication cost cannot be assessed nor compared to the cost of currently available oral iron formulations. The cost per tablet (US dollars) of oral iron salt formulations in the USA, all of which are administered one to three times daily, are as follows: ferrous fumarate: 0.22-0.39; ferrous gluconate: 0.04 -0.11; ferrous sulfate: 0.01-0.82.[40] All aforementioned oral iron salt formulations are currently available as over-the-counter medications, while Accrufer® (ferric maltol) will only be available as a prescription medication with intellectual property protection out to the year 2035.[28]

Clinical Implications

Ferric maltol (FM) is a non-salt oral iron replacement agent that is effective and displays a good tolerability profile in IDA patients with IBD or CKD. In a systematic review analyzing the tolerability of several oral iron supplements, the incidence of gastrointestinal (GI) AEs was 43% for ferrous fumarate, 30% for ferrous gluconate, and 30% for ferrous sulfate.[23] In FM's clinical trials, the incidence of GI AEs was approximately 25%, which may suggest better GI tolerability as compared to ferrous iron salts.[27] However, no head-to-head controlled trials comparing the tolerability of FM versus oral ferrous iron salts exist, thus it is difficult to make direct comparisons. The favorable GI tolerability can likely be attributed to the novel chemical and pharmacokinetic properties of FM as compared to traditional oral ferrous iron salt formulations such as ferrous sulfate, ferrous gluconate, and ferrous fumarate. In addition, through FM's high bioavailability as compared to ferrous iron preparations, this may allow relatively lower doses of elemental iron to be administered for treatment of ID, which might further reduce the risk of GI side effects. In clinical trials, FM was well-tolerated and demonstrated a similar overall incidence of AEs compared with placebo in patients that were unable to previously tolerate oral ferrous iron salt treatment.

Although there are encouraging results based on the aforementioned clinical trials, several limitations exist which may hinder FM's use in clinical practice. While clinical trials displayed tolerability and efficacy of FM for the treatment of iron deficiency anemia in IBD and CKD adult patients, the FDA granted broad approval of FM for the treatment of ID, with or without anemia, in adults.

The AEGIS-1 and AEGIS-2 studies, as well as the OLE, only included patients 18 years or older with quiescent IBD and IDA who have previously failed oral ferrous iron salt therapy.[24,25] The AEGIS-CKD study only included patients 18 years or older with non-dialysis dependent CKD and IDA.[37] Both studies only evaluated adult patients with mild-to-moderate anemia related to ID, as defined by meeting criteria for different combinations of both hemoglobin and iron parameter values. Given that severe anemia (i.e. Hb ≤7-8 g/dL) is an indication for IV iron treatment, this allows for better generalizability to the appropriate patient population utilizing oral iron therapies for treatment of IDA.[21] Iron deficiency, and specifically IDA, is not exclusive to any age group; every age group is vulnerable and includes patients with comorbidities beyond IBD or CKD. Iron deficiency is prevalent in rapidly growing children and adolescents, females of reproductive age, and pregnant patients. In contrast, postmenopausal women and adult men are at lower risks of ID because their diets are likely sufficient to cover their normal physiological iron requirements. These studies did not include pediatric patients, thus the safety and efficacy of FM seen in these studies should not be extrapolated to patients less than 18 years old. Given that women, especially women of reproductive age, are affected more often than men, another consideration is the age of the adults included in these studies. While the studies included a greater proportion of women than men, more than half of the participants were ≥65 years old, which might not be generalizable to the generally younger patient population affected by ID.

Table 4 | Common Adverse Events[27]

Event	Incidence
Flatulence	4.6%
Diarrhea	4.0%
Constipation	4.0%
Discoloration of feces	4.0%
Abdominal pain	2.9%
Nausea	1.7%
Vomiting	1.7%
Abdominal discomfort	1.1%
Abdominal distention	1.1%

Although pregnant patients were excluded in these studies, likely due to ethical concerns, maternal use of FM is not expected to result in fetal exposure because the FM complex is not absorbed systemically.[27] In embryofetal animal studies, pregnant animals did not experience any maternal toxicities or adverse developmental outcomes after administration of oral FM doses up to 32 times the recommended human dose.[27]

Despite these studies only including patients with either quiescent IBD or non-dialysis dependent CKD, these comorbidities represent patient populations largely affected by ID and IDA. Given that there is a potentially increased risk of GI tract inflammation with administration of oral iron preparations in patients with an active IBD flare, the AEGIS-1 and AEGIS-2 studies included what would typically be seen in clinical practice.[21,27] In the AEGIS-CKD study, they included IDA patients with CKD who were not dialysis-dependent, which represents the population of CKD patients that are more commonly treated with oral iron supplementation initially as opposed to dialysis-dependent CKD patients, who typically require IV iron therapy for treatment.[21] Although these studies showed promising results in IBD and CKD patients, further studies should be conducted in patients with different comorbidities or chronic inflammatory conditions to examine the efficacy and tolerability of FM in patients with other disease states that commonly complicated by ID or IDA.

Additionally, in the clinical trials used for FDA approval, FM was compared to a matched oral placebo. The use of a placebo control treatment arm instead of an active comparator limits the comparability of the aforementioned findings. To date, there are no head-to-head comparisons of FM versus oral ferrous iron salt formulations and there are currently no ongoing head-to-head comparisons to compare efficacy and tolerability between oral iron formulations. While AEGIS-1 and AEGIS-2 studies were not head-to-head trials, FM demonstrated efficacy and tolerability in IBD patients who had previously failed treatment with oral ferrous iron salts, mainly for reasons such as intolerability or lack of efficacy.[24,25] The data from these studies suggest that FM might demonstrate a more favorable GI tolerability profile as opposed

to oral ferrous iron salts in patients who are more sensitive to GI AEs and have a higher predisposition to experience intolerance to oral iron agents.

In the AEGIS-1, AEGIS-2, and AEGIS-H2H studies, health-related quality of life (QoL) was assessed.[24,25,38] Of note, the AEGIS-H2H post-hoc analysis demonstrated non-statistically significant improvements in health-related QoL scores (assessed using the 36-item Short Form questionnaire) in both FM and IV FCM treatment groups, with no statistically significant differences between treatment groups.[38] This indicates there was at least no decline in patient QoL with FM treatment during the study period.

Ferric maltol does not offer any added benefit in terms of ease of administration as compared to ferrous iron salts. Ferric maltol is administered twice daily, while oral ferrous iron salts are administered two to three times daily depending on patient tolerability. Like other oral iron formulations, FM is recommended to be administered on an empty stomach and separated from meals by one to two hours to improve absorption.

To date, there is one head-to-head active comparator study comparing the safety and efficacy of oral FM versus IV FCM for the treatment of IDA in IBD patients for 12 weeks, which also included a long-term safety and efficacy study period. Considering the results of the AEGIS-H2H study have yet to be published and peer-reviewed, data should be extrapolated, if at all, with caution. Initial clinical trial data originally suggested FM demonstrated efficacy in treating IDA in IBD patients where FM was found to be noninferior to IV ferric carboxymaltose.[38] This conclusion was based on the per protocol analysis of the primary endpoint of the study, defined as hemoglobin normalization or a ≥2 g/dL increase in hemoglobin at week 12.[38] In the ITT analysis, FM did not achieve noninferiority compared to IV FCM for the primary endpoint.[41] Of note, the study's pre-defined success criteria to achieve noninferiority required that noninferiority is achieved in both the PP and ITT analyses in order for FM to be considered noninferior to IV FCM. Based off of this initial data and the pre-defined noninferiority success criteria, FM did not achieve noninferiority compared to IV FCM at the primary endpoint.[41] This prompted the pharmaceutical company to initiate an independent review and analysis of both datasets.[41] A recent press release from Shield Therapeutics reported that a reanalysis of the data revealed that FM did not achieve noninferiority in either the PP or ITT populations at the primary endpoint, but FM-treated patients still displayed clinically significant increases in hemoglobin levels which were maintained in the long-term study phase.[42] Of note, the primary endpoint results presented in the aforementioned AEGIS-H2H section reflect the most updated findings at the time of this writing. Despite the conflicting data for the primary endpoint, it is important to take into consideration the rate which the Hb normalization was achieved and in which patients when comparing oral and IV iron supplementation. Intravenous FCM achieved a higher rate of Hb concentration normalization at week 4 in all patients, as well as in patients specifically with a Hb concentration <9.5 g/dL, in comparison to oral FM.[38] When making treatment decisions regarding iron replacement, it is important to consider this difference in time to normalization, the severity of the patient's anemia, and whether oral FM is clinically appropriate for the patient as opposed to an IV iron formulation.

Conclusion

Accrufer® (ferric maltol) is a novel non-salt oral formulation of ferric (Fe3+) iron that achieved broad FDA approval in July 2019 for the treatment of iron deficiency in adults. In the AEGIS clinical trial series FM demonstrated efficacy in correcting IDA and improving serum iron parameters, including ferritin and TSAT. Ferric maltol also displayed efficacy and improved tolerability in IBD patients who experienced inefficacy or intolerance on previous treatment with oral ferrous iron salts. Emerging data comparing the efficacy of FM to IV iron supplementation is conflicting, but currently indicates that FM did not demonstrate noninferiority to IV iron therapy. This medication appears to be well tolerated with the most common adverse effects being gastrointestinal in nature and of mild to moderate severity. At this time, the true place in therapy for FM is not yet determined, however it does appear to be a suitable alternative therapy in those with iron deficiency who are unable to tolerate oral ferrous iron salts.

References

1. McDowell LR. 2nd ed. Amsterdam: Elsevier Science; 2003. Minerals in Animal And Human Nutrition; p. 660.
2. World Health Organization. Micronutrient deficiencies [Internet]. [cited 2020 Aug 25]. Available from: https://www.who.int/nutrition/topics/ida/en/
3. Ludwig H, Müldür E, Endler G, et al. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol. 2013;24(7):1886-1892. doi:10.1093/annonc/mdt118
4. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis. 2013;7(1):1-33. doi:10.1016/j.crohns.2012.09.005
5. Hsu CY, McCulloch CE, Curhan GC. Iron status and hemoglobin level in chronic renal insufficiency. J Am Soc Nephrol. 2002;13(11):2783-2786. doi:10.1097/01.asn.0000034200.82278.dc
6. Okonko DO, Mandal AK, Missouris CG, et al. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. J Am Coll Cardiol. 2011;58(12):1241-1251. doi:10.1016/j.jacc.2011.04.040
7. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013;165(4):575-582.e3. doi:10.1016/j.ahj.2013.01.017
8. Wood RJ, Ronnenberg A. Iron. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern Nutrition in Health And Disease. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2005. Pp. 248–70.
9. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci. 2014;19(2):164-174.
10. Dallman P. Iron. In: Brown ML, editor. Present Knowledge in Nutrition. 6th ed. Washington DC: Nutrition Foundation; 1990. Pp. 241–50.
11. Enjuanes C, Klip IT, Bruguera J, et al. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. Int J Cardiol. 2014;174(2):268-275. doi:10.1016/j.ijcard.2014.03.169
12. "Iron-Deficiency Anemia." National Heart Lung and Blood Institute, U.S. Department of Health and Human Services, 18 Jan. 2019, www.nhlbi.nih.gov/health-topics/iron-deficiency-anemia

13. Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr. 2001;131(2S-2):676S-690S. doi:10.1093/jn/131.2.676S
14. Patterson AJ, Brown WJ, Powers JR, et al. Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. Qual Life Res. 2000;9 (5):491-497. doi:10.1023/a:1008978114650
15. Beard JL, Hendricks MK, Perez EM, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr. 2005;135(2):267-272. doi:10.1093/jn/135.2.267
16. Kovesdy CP, Estrada W, Ahmadzadeh S, et al. Association of markers of iron stores with outcomes in patients with nondialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(2):435-441. doi:10.2215/CJN.03980808
17. Thurnham DI, McCabe LD, Haldar S, et al. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta -analysis. Am J Clin Nutr. 2010;92(3):546-555. doi:10.3945/ajcn.2010.29284
18. Camaschella C. Iron deficiency: new insights into diagnosis and treatment. Hematology Am Soc Hematol Educ Program. 2015;2015:8-13. doi:10.1182/asheducation-2015.1.8
19. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010;116(23):4754-4761. doi:10.1182/blood-2010-05-286260
20. Clénin GE. The treatment of iron deficiency without anaemia (in otherwise healthy persons). Swiss Med Wkly. 2017;147:w14434. Published 2017 Jun 14. doi:10.4414/smw.2017.14434
21. Camaschella, Clara. "Iron Deficiency." Blood, vol. 133, no. 1, 2019, pp. 30–39., doi:10.1182/blood-2018-05-815944.
22. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383. Published 2015 Feb 20. doi:10.1371/journal.pone.0117383
23. Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, et al. Tolerability of different oral iron supplements: a systematic review. Curr Med Res Opin. 2013;29(4):291-303. doi:10.1185/03007995.2012.761599
24. Gasche C, Ahmad T, Tulassay Z, et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. Inflamm Bowel Dis. 2015;21(3):579-588. doi:10.1097/MIB.0000000000000314
25. Schmidt C, Ahmad T, Tulassay Z, et al. Ferric maltol therapy for iron deficiency anaemia in patients with inflammatory bowel disease: long-term extension data from a Phase 3 study. Aliment Pharmacol Ther. 2016;44(3):259-270. doi:10.1111/apt.13665
26. Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician. 2013;87(2):98-104.
27. Accrufer. Package insert. Shield Therapeutics; 2019.
28. Shield Therapeutics PLC. FDA approves Accrufer® with a broad label of treating iron deficiency in adults [press release]. Published July 26, 2019. Accessed August 31, 2020. https://www.shieldtherapeutics.com/wp-content/uploads/2019/07/STX-Feraccru-FDA-approval-26.07.19.pdf
29. Harvey RS, Reffitt DM, Doig LA, et al. Ferric trimaltol corrects iron deficiency anaemia in patients intolerant of iron. Aliment Pharmacol Ther. 1998;12:845-848. doi:10.1046/j.1365-2036.1998.00380.x
30. Singh RK, Barrand MA. Lipid-peroxidation effects of a novel iron compound, ferric maltol—a comparison with ferrous sulfate. J Pharm Pharmacol. 1990;42:276-279. doi:10.1111/j.2042-7158.1990.tb05407.x
31. Stallmach A, Buning C. Ferric maltol (ST10): a novel oral iron supplement for the treatment of iron deficiency anemia in inflammatory bowel disease. Expert Opin Pharmacother. 2015;16:2859-2867. doi:10.1517/14656566.2015.1096929
32. Barrand MA, Callingham BA, Hider RC. Effects of the pyrones, maltol and ethyl maltol, on iron absorption from the rat small intestine. J Pharm Pharmacol. 1987;39(3):203-211. doi:10.1111/j.2042-7158.1987.tb06249.x
33. Barrand MA, Callingham BA, Dobbin P, et al. Dissociation of a ferric maltol complex and its subsequent metabolism during absorption across the small intestine of the rat. Br J Pharmacol. 1991;102(3):723-729. doi:10.1111/j.1476-5381.1991.tb12240.x
34. Kelsey SM, Hider RC, Bloor JR, et al. Absorption of low and therapeutic doses of ferric maltol, a novel ferric iron compound, in iron deficient subjects using a single dose iron absorption test. J Clin Pharm Ther. 1991;16(2):117-122. doi:10.1111/j.1365-2710.1991.tb00292.x
35. Lund EK, Wharf SG, Fairweather-Tait SJ, et al. Oral ferrous sulfate supplements increase the free radical-generating capacity of feces from healthy volunteers [published correction appears in Am J Clin Nutr. 2003 Sep;78(3):498]. Am J Clin Nutr. 1999;69(2):250-255. doi:10.1093/ajcn/69.2.250
36. Bokemeyer B, Krummenerl A, Maaser C, et al. Randomized Open-Label Phase 1 Study of the Pharmacokinetics of Ferric Maltol in Inflammatory Bowel Disease Patients with Iron Deficiency. Eur J Drug Metab Pharmacokinet. 2017;42 (2):229-238. doi:10.1007/s13318-016-0334-5
37. Kopyt N. Efficacy and safety of oral ferric maltol (FM) in treating iron-deficiency anemia (IDA) in patients with CKD: randomized controlled trial. J Am Soc Nephrol. 2018;29:70-71.
38. Howaldt S. Oral ferric maltol versus intravenous ferric carboxymaltose for the treatment of iron-deficiency anaemia in patients with inflammatory bowel disease: a multicenter phase 3b, open-label randomised controlled trial. United European Gastroenterol J. 2019;7.
39. WHO. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Vitamin and Mineral Nutrition Information system (WHO/NMH/NHD/MNM/111). Geneva, Switzerland: World Health Organization; 2011. Accessed August 24, 2020. https://www.who.int/vmnis/indicators/haemoglobin.pdf
40. Lexicomp Online. Lexi-Drugs. Wolters Kluwer Clinical Drug Information; 2020
41. Shield Therapeutics PLC. AEGIS-H2H study update [press release]. Published March 17, 2020. Accessed August 31, 2020. https://www.shieldtherapeutics.com/rns_news/aegis-h2h-study-update/
42. Shield Therapeutics PLC. AEGIS-H2H study reanalysis [press release]. Published August 6, 2020. Accessed August 31, 2020. https://www.shieldtherapeutics.com/wp-content/uploads/2020/08/RNS-H2H-reanalysis-FINAL.pdf

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida