LIFE IS FULL OF IRONY

Your patients don't need it in their iron

Rather than helping them feel better, traditional oral irons can make most patients feel worse. Introducing ACCRUFeR: the only FDA-approved oral iron for all adults with ID/IDA. It's both tolerable and effective, so it can actually do what it's supposed to do.[1-3]

ID, iron deficiency;
IDA, iron-deficiency anemia.

ACCRUFeR®
(ferric maltol) *30 mg capsules*

The Un-ironic Iron

INDICATIONS AND USAGE

ACCRUFeR is indicated for the treatment of iron deficiency in adults.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ACCRUFeR is contraindicated in patients with a history of:

- Hypersensitivity to ACCRUFeR or any of its inactive components
- Hemochromatosis and other iron overload syndromes
- Receiving repeated blood transfusions as this may result in iron overload

Please see Important Safety Information throughout and accompanying full Prescribing Information.

People with ID and IDA need effective treatments

In the United States, **~10M people have ID** and **~5M people have IDA**[4]

Prevalence is highest in patients with inflammatory conditions and in people of childbearing age:*

	ID	IDA
Women's health conditions (eg, menorrhagia, pregnancy, uterine fibroids)[5]	~66%[6]	Up to 75%[7]
IBD (eg, Crohn's, UC)	36%-90%[8]	36%-76%[9]
CKD	20%-65%[10]	11%-27%[10]

- Heart failure, surgery, and cancer are also associated with higher rates of ID and IDA[11]
- ID and IDA are also prevalent in people with malabsorption, nutritional deficits, and restrictive diets[11]

*Prevalence estimates differ due to the disease stage and severity of the patient population being studied.

CKD, chronic kidney disease; IBD, inflammatory bowel disease; M, million; UC, ulcerative colitis.

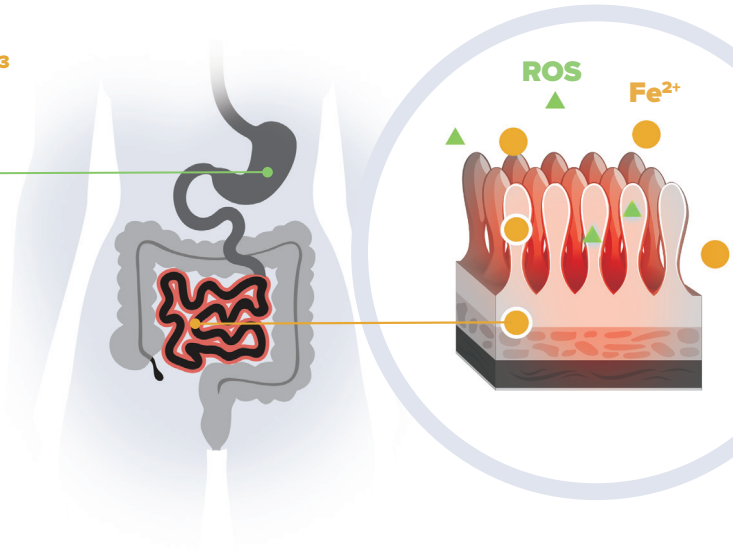
TESTING FOR AND DIAGNOSING ID AND IDA ARE CRUCIAL FOR YOUR PATIENTS WITH THESE CONDITIONS

GI side effects are a barrier to staying on oral iron treatment for many patients[12]

The limitations of traditional oral irons such as ferrous salts (Fe^{2+}) lead to GI side effects[13-15]

90% of Fe^{2+} in ferrous salts goes unabsorbed[13]

When ferrous salts **dissociate in the stomach**, the unabsorbed Fe^{2+} oxidizes, which generates ROS[13-15]



The ROS can then cause **irritation and damage** when they reach the intestinal lining[13-15]

Up to 70% of people taking traditional oral iron report GI issues such as[1,2]:

- Heartburn
- Nausea
- Flatulence
- Loss of appetite
- Diarrhea
- Constipation
- Stomach cramps
- Discolored stool

Up to **60%** of patients will discontinue treatment due to adverse reactions[16]

GI, gastrointestinal; ROS, reactive oxygen species.

ORAL IRON SHOULD HELP PATIENTS FEEL BETTER, NOT WORSE.

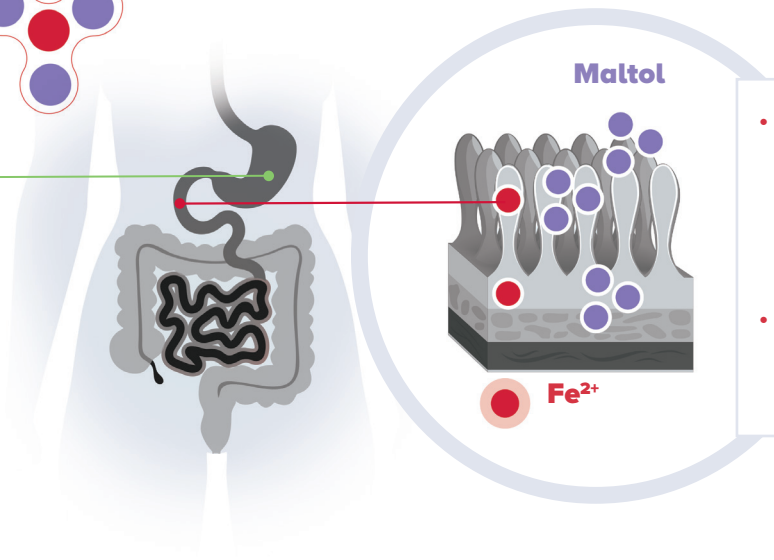
THE IRONY ISN'T LOST ON US

It's time for iron without the irony

ACCRUFeR is the only non-salt ferric iron uniquely formulated with maltol, leading to demonstrated absorption in the GI tract[3,15]

ACCRUFeR (ferric maltol)

The **maltol shields the iron**, which creates a complex that stays intact as it passes through the stomach[3,15]



- Because of this unique shielding, the iron remains highly bioavailable when it reaches the **duodenum, where it is absorbed**[3]
- The shielding also reduces the likelihood of ROS formation and GI side effects[15]

FERRIC MALTOL IS DESIGNATED AS A NEW CHEMICAL ENTITY, WHICH PUTS ACCRUFeR IN A CLASS OF ITS OWN[17]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Increased Risk of Inflammatory Bowel Disease (IBD) Flare

Avoid use of ACCRUFeR in patients with an active IBD flare, as there is potential risk of increased inflammation in the gastrointestinal tract.

Iron Overload

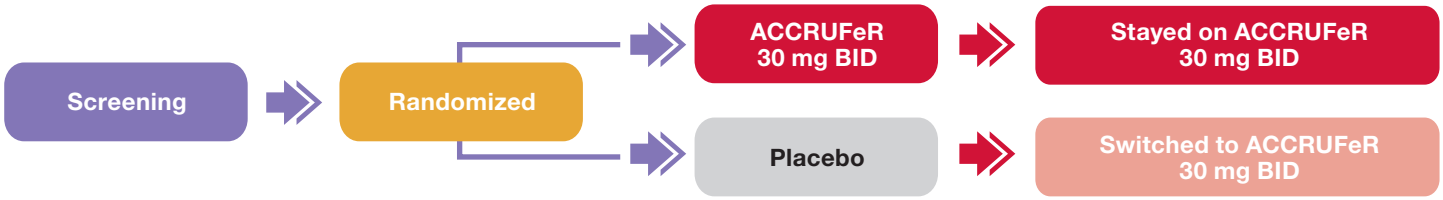
Excessive therapy with iron products can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Do not administer ACCRUFeR to patients with evidence of iron overload or patients receiving intravenous iron. Assess iron parameters prior to initiating ACCRUFeR and monitor iron parameters while on therapy .

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

The only FDA-approved oral iron for all adults with ID/IDA, regardless of underlying condition[3]

ACCRUFeR is backed by a robust clinical profile from clinical studies in difficult-to-treat patients[3]

The AEGIS studies in IBD and CKD were phase 3A, randomized, double-blind, placebo-controlled trials with an open-label extension phase[18,19]



AEGIS IBD STUDY DESIGN

- 128 IBD patients (58 ulcerative colitis, 70 Crohn's disease) with IDA across 2 studies were randomized 1:1[3]
- Hb concentrations were between 9.5 g/dL and 12/13 g/dL for females/males and ferritin <30 g/dL. All patients had previously failed on treatment with oral ferrous replacement products[3]
- A responder analysis was done defining treatment responders as patients who achieved increases in Hb of ≥1 g/dL or ≥2 g/dL, or Hb normalization by Week 12. Normalization of Hb was defined based on Hb values ≥12 g/dL for females or ≥13 g/dL for males[14,18]

STUDY ENDPOINTS

- **Primary endpoint:** Mean difference in Hb concentration from baseline to Week 12 between ACCRUFeR and placebo. The LS mean difference from baseline was 2.18 g/dL (P<0.0001)[3]
- **Secondary endpoints:** Changes in Hb concentration from baseline to Weeks 4 and 8, serum ferritin concentration, and TSAT[3]

POPULATION BASELINE CHARACTERISTICS

- **Mean age:** 38.5 (placebo) to 40.1 (ACCRUFeR) years[14]
- **Gender and ethnicity:** 45 males and 83 females; 122 white and 6 other[14]

AEGIS CKD STUDY

- 167 stage 3-4 CKD patients with IDA were randomized 2:1 (ACCRUFeR to placebo)[19]

STUDY ENDPOINTS

- **Primary endpoint:** The mean difference in Hb concentration from baseline to Week 16 between ACCRUFeR and placebo[19]
- **Secondary endpoints:** Proportions of patients with Hb increases of ≥1 g/dL and ≥2 g/dL at Week 16; the proportion of patients achieving a Hb concentration of ≥11.0 g/dL at Week 16; change in Hb concentration from baseline to Weeks 4 and 8; and changes in ferritin, TSAT, and serum iron measures at Weeks 4, 8, and 16[19]

POPULATION BASELINE CHARACTERISTICS

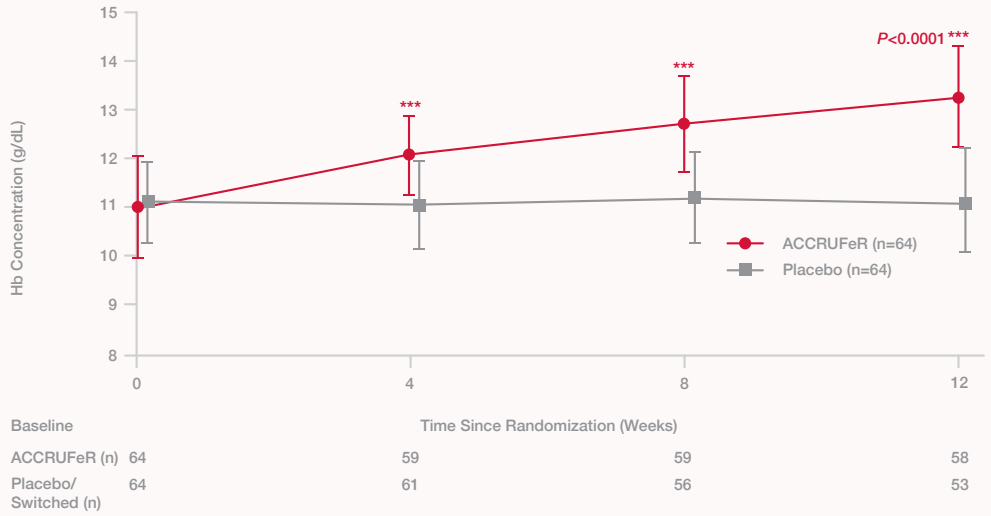
- **Mean age:** 65.2 (placebo) to 68.5 (ACCRUFeR) years, range 30-90 years[3,19]
- **Gender and ethnicity:** 50 males and 117 females; 123 White, 35 African American, and 9 other[3,19]

BID, twice a day; FDA, US Food and Drug Administration; Hb, hemoglobin; LS, least squares; TSAT, percentage transferrin saturation.

ACCRUFeR® (ferric maltol) 30 mg capsules

Significant and rapid improvements were seen in difficult-to-treat patients with IBD[14]

Primary endpoint: Mean (SD) Hb concentration from baseline to Week 12[14]



The mean (SE) improvement in Hb in the ACCRUFeR group vs placebo was **2.25** (0.12) g/dL (one-sided 97.5% CI, 1.81; *P*<0.0001 based on ANCOVA).[14]

Statistical significance was achieved as early as **Week 4**.[14]

of patients taking ACCRUFeR saw a ≥1 g/dL change in Hb at Week 12[14]*

VS

of patients in the placebo group saw a ≥1 g/dL change in Hb at Week 12[14]*

ACCRUFeR increased ferritin levels and TSAT[14]

- The mean (SD) overall increase in serum ferritin for patients taking ACCRUFeR was **17.3** (28.30) µg/L compared with 1.2 (7.85) µg/L for the placebo group
- Patients taking ACCRUFeR saw a mean (SD) increase of **18.0%** (20.2) in TSAT compared with a small reduction (-0.4% [7.8]) in patients in the placebo group

*According to responder analysis.

ANCOVA, analysis of covariance; CI, confidence interval; SD, standard deviation; SE, standard error.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

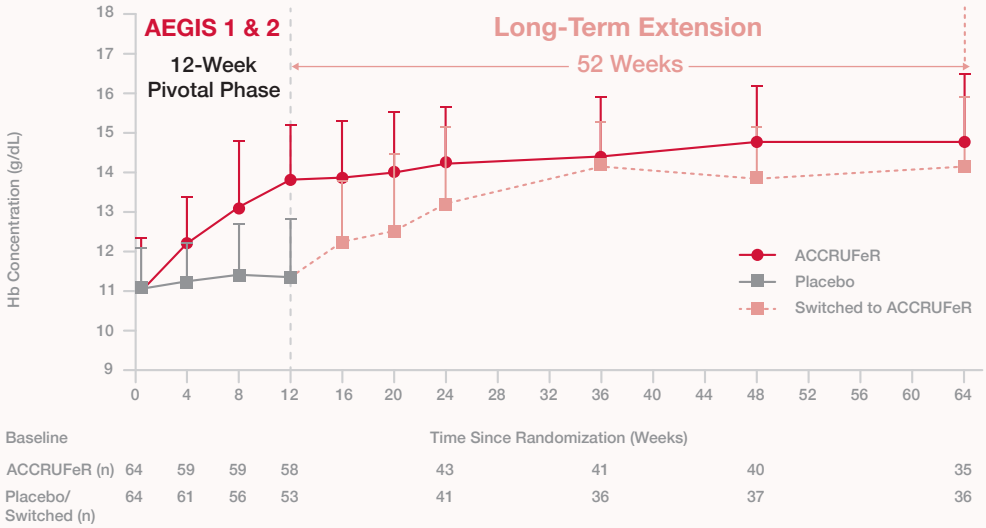
Risk of Overdosage in Children Due to Accidental Ingestion

Accidental overdose of iron products is a leading cause of fatal poisoning in children under age 6. Keep out of reach of children.

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

Long-term improvements continued over 64 weeks[18]

Absolute Hb concentrations from baseline (Day 0) to 64 weeks[18]



Baseline																
ACCRUFeR (n)	64	59	59	58				43				41			40				35
Placebo/ Switched (n)	64	61	56	53				41				36			37				36

ACCRUFeR:
Mean improvement in Hb concentration was **3.07** (1.46) g/dL from baseline to Week 64.[18]

PLACEBO/SWITCHED:
Mean improvement in Hb concentration was **2.19** (1.61) g/dL from baseline to Week 64.[18]

- The cumulative proportion of patients who maintained normal Hb was 71% at Week 12, 79.7% at Week 24, and 86.1% at Week 64[18]
- TSAT increased from 10% at baseline to 26% at Week 16 and 29% at Week 64[18]

Very high median overall compliance across short and long-term clinical studies[18]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

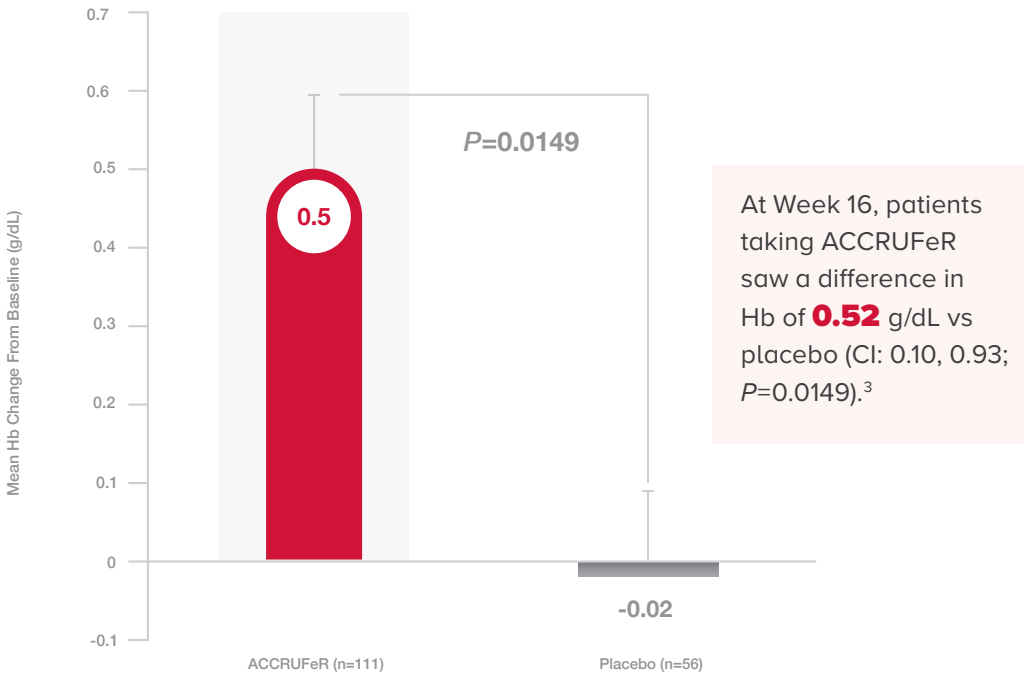
Most common adverse reactions (≥1%) reported with ACCRUFeR during the double-blind, placebo-controlled portions of the pivotal trials were flatulence, diarrhea, constipation, feces discolored, abdominal pain, nausea, vomiting, and abdominal discomfort/distension.

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

ACCRUFeR® (ferric maltol) 30 mg capsules

Significant improvements were seen across iron measures in patients with stage 3 and 4 CKD[3,19]

Primary endpoint: Mean (SE) change in Hb at Week 16[3]



At Week 16, patients taking ACCRUFeR saw a difference in Hb of **0.52** g/dL vs placebo (CI: 0.10, 0.93; *P*=0.0149).[3]

- ACCRUFeR had an LS mean difference in change from baseline Hb of 0.13 g/dL at Week 4 and 0.46 g/dL at Week 8 vs placebo[3]
- Increases in Hb for patients taking ACCRUFeR at Weeks 4, 8, and 16 were consistent with changes seen in the AEGIS-IBD studies[14,19]

ACCRUFeR increased ferritin levels and TSAT

- The mean change in ferritin concentration from baseline to Week 16 was 49.3 mcg/L for the ACCRUFeR group and 6.3 mcg/L for the placebo group, with a mean difference of **43.0** mcg/L (*P*<0.001)[3,19]
- The mean percent change in TSAT saturation from baseline (LS mean, SE) was 3.8 (0.6) for the ACCRUFeR group and -0.9 (0.9) for the placebo group, with a mean difference of **4.6** (1.1) (*P*<0.001)[19]

IMPORTANT SAFETY INFORMATION

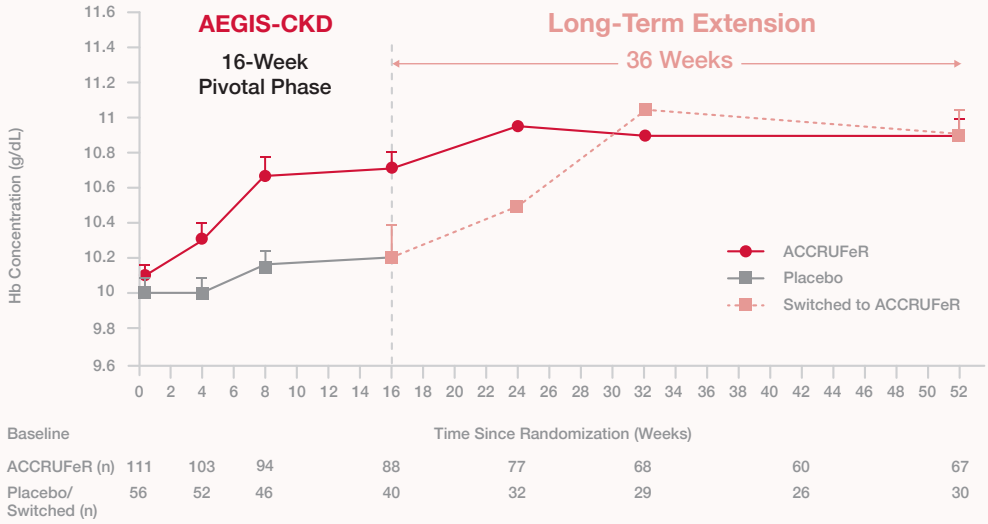
ADVERSE REACTIONS

To report adverse events, please contact Shield Therapeutics at 1-888-963-6267. You may also contact the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

Improvements in Hb were maintained over 52 weeks[19]

Absolute (SE) Hb concentrations in patients over time[19]



ACCRUFeR:
Mean improvement in Hb concentration was **0.7** (1.7) g/dL from baseline to Week 52.[19]

PLACEBO/SWITCHED:
Mean improvement in Hb concentration was **0.5** (1.4) g/dL from baseline to Week 52.[19]

74% **of patients taking ACCRUFeR completed the the year-long extension phase[19]**

PATIENTS WITH CKD SAW BOTH SHORT-TERM AND LONG-TERM IMPROVEMENT IN HB WITH ACCRUFeR[19]

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

- Avoid concomitant use with dimercaprol
- Separate administration of ACCRUFeR from certain oral medications where interaction might occur. Monitor clinical responses as appropriate

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

ACCRUFeR®
(ferric maltol) 30 mg capsules

In a class of its own with established safety and unprecedented tolerability[3,14]

ACCRUFeR is a new chemical entity that is uniquely formulated for improved absorption[3,15,17]

With ACCRUFeR, the iron is shielded with maltol, which prevents it from dissociating in the stomach and generating ROS.[3,15]

4.6% Only **4.6%** of patients discontinued **ACCRUFeR** due to adverse reactions[3]*

- Neither short- nor long-term ACCRUFeR treatment led to iron overload[3]

Adverse reactions reported by ≥1% of patients treated with ACCRUFeR during double-blind phases of placebo-controlled period of pooled studies (AEGIS IBD and AEGIS CKD)[3]

Body System Adverse Reaction Gastrointestinal	**ACCRUFeR** 30 mg bid (N=175)	**Placebo** (N=120)
Flatulence	4.6%	0%
Diarrhea	4%	1.7%
Constipation	4%	0.8%
Discolored feces	4%	0.8%
Abdominal pain	2.9%	2.5%
Nausea	1.7%	0.8%
Vomiting	1.7%	0%
Abdominal discomfort	1.1%	0%
Abdominal distention	1.1%	0%

*Excluding the open-label extension period.

INDIVIDUAL GI ADVERSE REACTIONS WERE REPORTED BY <5% OF PATIENTS[3]

The lowest dose of elemental iron proven to successfully reverse IDA[3,15]

Because the iron in ACCRUFeR is highly bioavailable, a low dose of 30 mg twice daily can be used, which further minimizes the potential for adverse reactions[3,15]

Patients take one
30-mg capsule twice daily
without food[3]

Treatment considerations[3]

- Advise patients to take ACCRUFeR 1 hour before or 2 hours after a meal
- Treatment duration depends on the severity of iron deficiency; at least 12 weeks of treatment is typically required
- Treatment with ACCRUFeR should be continued for as long as necessary until ferritin levels are within the normal ranges

PRESCRIPTIONS FOR STOOL SOFTENER OR OTHER SUPPLEMENTS ARE NOT REQUIRED. ACCRUFeR CAN BE TAKEN ON ITS OWN[3,20]

A commitment to affordability for patients

At Shield Therapeutics, we believe that ACCRUFeR will revolutionize the standard of care in ID/IDA

That's why we are dedicated to ensuring that patients can start treatment right away and pay the lowest price possible on their prescriptions.

Eligible patients pay no more than $25 per month for an FDA-approved treatment

PATIENTS WITH COMMERCIAL INSURANCE

Free 30-day supply:

- Available immediately for eligible patients regardless of whether or not a prior authorization (PA) is required

Pay $0 or $25:

- If a PA is required and approved by insurance, your patient will continue to have a $0 copay for refills
- If a PA is required but not approved by insurance, your patient will still have access to therapy with only a $25 copay for refills

PATIENTS WITH MEDICARE PART D

Pay $25:

- All patients are automatically eligible for a $25 cash price for first fill and subsequent refills

PATIENTS WITH MEDICAID

- Coverage and copays vary by state

PA, prior authorization.

Learn more

We've partnered with BlinkRx to better serve our patients

BlinkRx is an innovative e-pharmacy that helps streamline the prescription process

BlinkRx helps your patients and your staff every step of the way, from initial prescription to subsequent refills. Our goal is to get your patients started with ACCRUFeR as smoothly as possible, and to help them stay adherent to therapy.

BLINKRX ADVANTAGES INCLUDE:

PA SUPPORT

Practice Access Managers can help you customize your preferences to simplify the initial PA submission. From there, a support team will be available to assist your staff throughout the process.

STREAMLINED EXPERIENCE

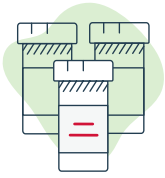
BlinkRx will find the lowest available price and notify your patients via text so they can simply purchase it online or over the phone.

FREE, FAST DELIVERY

BlinkRx will deliver ACCRUFeR to your patients for free from one of their 7,000+ licensed pharmacy partners.

AUTOMATIC REFILLS

Patients can opt in to automatic refills through BlinkRx so they never miss a dose.



BlinkRx is already available in your EMR.
E-prescribe ACCRUFeR to BlinkRx U.S. Boise, Idaho

Phone: 1 (844) 926-2480
Fax: 1 (866) 585-4631

DAW, dispense as written; EMR, electronic medical record; PO, by mouth.

IRON WITHOUT THE IRONY

- **The only FDA-approved** oral iron for all adults with ID/IDA, regardless of underlying condition[3]
- **In a class of its own** with its unique formulation and demonstrated absorption[3,14,15]
- **Unprecedented tolerability and significant results** seen in multiple studies in difficult-to-treat patients[3]
- **Fast and affordable access** through BlinkRx helps your patients save on prescriptions

Show your patients the possibilities of The Un-ironic Iron

Learn more

INDICATIONS AND USAGE

ACCRUFeR® (ferric maltol) is indicated for the treatment of iron deficiency in adults.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ACCRUFeR is contraindicated in patients with a history of:

- Hypersensitivity to ACCRUFeR or any of its inactive components
- Hemochromatosis and other iron overload syndromes
- Receiving repeated blood transfusions as this may result in iron overload

Please see Important Safety Information throughout and accompanying full ACCRUFeR Prescribing Information.

References: 1. DeLoughery TG. Safety of oral and intravenous iron. *Acta Haematol.* 2019;142(1):8-12. doi:10.1159/000496966. **2.** Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One.* **3.** ACCRUFeR® full prescribing information. Shield Therapeutics, 2022. **4.** Miller JL. Iron deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med.* 2013;3:a011866. **5.** Friedman AJ, Chen Z, Ford P, et al. Iron deficiency anemia in women across life span. *J Womens Health (Larchmt).* 2012;21(12):1282-1289. **6.** Camaschalla C. Iron deficiency. *Blood.* 2019;133(1):30-39. doi:10.1182/blood-2018-05-815944. **7.** Mirza FG, Abdul-Kadir R, Breymann C, Fraser IS, Taher A. Impact and management of iron deficiency and iron deficiency anemia in women's health. *Expert Rev Hematol.* 2018;11(9):727-736. doi: 10.1080/17474086.2018.1502081. **8.** Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther.* 2006;24(11-12):1507-1523. **9.** Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol.* 2010;7(11):599-610. **10.** Fishbane S, Pollack S, Feldman HI, Joffe MM, et al. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988–2004. *Clin J Am Soc Nephrol.* 2009;4(1):57-61. **11.** Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. *J Intern Med.* 2020;287(2):153-170. doi:10.1111/joim.13004. **12.** Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol.* 2009;44(7):838-845. doi:10.1080/00365520902839667. **13.** Howaldt S, Domènech E, Martinez N, Schmidt C, Bokemeyer B. Long-term effectiveness of oral ferric maltol vs intravenous ferric carboxymaltose for the treatment of iron-deficiency anemia in patients with inflammatory bowel disease: A randomized controlled noninferiority trial. *Inflamm Bowel Dis.* 2021;28(3):373-384. doi:10.1093/ibd/izab073. **14.** Gasche C, Ahmad T, Tulassay Z, et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2015;21(3):579-588. doi:10.1097/mib.0000000000000314. **15.** Stallmach A, Büning 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(18):2859-2867. doi:10.1517/14656566.2015.1096929. **16.** 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. **17.** Data on file. Shield Therapeutics Inc. 2019. **18.** 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. **19.** Pergola PE, Kopyt NP. Oral ferric maltol for the treatment of iron-deficiency anemia in patients with CKD: A randomized trial and open-label extension. *Am J Kidney Dis.* 2021;78(6):846-856. doi:10.1053/j.ajkd.2021.03.020. **20.** Iron caps with stool softener. Windmill Health Products. https://www.windmillvitamins.com/product/iron-caps-with-stool-softener. Accessed January 12, 2023.

shield therapeutics

ACC-US-00136 03/2023

ACCRUFeR® (ferric maltol) 30 mg capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACCRUFER® safely and effectively. See full prescribing information for ACCRUFER.

ACCRUFER (ferric maltol) capsules, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
ACCRUFER is an iron replacement product indicated for the treatment of iron deficiency in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- 30 mg twice daily on an empty stomach (2.1)
- Continue as long as necessary to replenish body iron stores (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 30 mg (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to the active substance or any excipient (4)
- Hemochromatosis and other iron overload syndromes (4)
- Patients receiving repeated blood transfusions (4)

----------WARNINGS AND PRECAUTIONS----------
- IBD flare: Avoid use in patients with IBD flare (5.1)
- Iron overload: Accidental overdose of iron products is a leading cause of fatal poisoning in children under 6. Keep out of reach of children. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 1%) are flatulence, diarrhea, constipation, feces discolored, abdominal pain, nausea, vomiting and abdominal discomfort/distension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shield Therapeutics Inc at 1-888-963-6267 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Dimercaprol: Avoid concomitant use. (7.2)
- Oral Medications: Separate administration of ACCRUFER from certain oral medications. Monitor clinical responses as appropriate. (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ACCRUFER is indicated for the treatment of iron deficiency in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ACCRUFER is 30 mg twice daily, taken 1 hour before or 2 hours after a meal. Do not open, break, or chew ACCRUFER capsules.

Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks of treatment is required. The treatment should be continued as long as necessary until ferritin levels are within the normal range.

3 DOSAGE FORMS AND STRENGTHS

Capsules: ACCRUFER contains 30 mg iron, as ferric maltol, in red capsules printed with “30”.

4 CONTRAINDICATIONS

ACCRUFER is contraindicated in patients with a history of:

- Hypersensitivity to the active substance or to any of the excipients *[see Description (11)].* Reactions could include shock, clinically significant hypotension, loss of consciousness, and/or collapse.
- Hemochromatosis and other iron overload syndromes *[see Warnings and Precautions (5.1)].* Use may result in iron overdose *[see Overdosage (10)].*
- Receiving repeated blood transfusions. Use may result in iron overload *[see Warnings and Precautions (5.2) and Overdosage (10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Inflammatory Bowel Disease (IBD) Flare

Avoid use of ACCRUFER in patients with an active inflammatory bowel disease (IBD) flare, as there is potential risk of increased inflammation in the gastrointestinal tract.

5.2 Iron Overload

Excessive therapy with iron products can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Do not administer ACCRUFER to patients with evidence of iron overload or patients receiving intravenous iron *[see Contraindications (4)]*. Assess iron parameters prior to

initiating ACCRUFER and monitor iron parameters while on therapy *[see Overdosage (10) and Clinical Pharmacology (12.2)]*.

5.3 Risk of Overdosage in Children Due to Accidental Ingestion

Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Inflammatory Bowel Disease Flare *[see Warnings and Precautions (5.1)]*
- Iron Overload *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ACCRUFER in 175 patients in the placebo-controlled phase of three randomized studies conducted in patients with anemia and quiescent inflammatory bowel disease (IBD) (Studies AEGIS 1 & 2) or non-dialysis dependent chronic kidney disease (CKD) (AEGIS 3). The pooled patient population had a mean age of 58 years, 67.4% were female (n=118), and 81.7% (n=143) were Caucasian.

Table 1 presents all adverse reactions occurring in the placebo-controlled period of the pooled randomized studies *[see Clinical Studies (14)]* occurring at a rate of > 1% in the treated group, and for which the rate for ACCRUFER exceeds the rate for placebo.

Table 1. Adverse Reactions Reported by ≥1% of Patients Treated with ACCRUFER During Placebo-Controlled Period of Pooled Studies (Studies AEGIS 1 & 2 and AEGIS 3)

	ACCRUFER 30 mg bid (N = 175)	**Placebo (N = 120)**
Body System Adverse Reaction		
Gastrointestinal		
Flatulence	4.6%	0%
Diarrhea	4%	1.7%
Constipation	4%	0.8%
Feces discolored	4%	0.8%
Abdominal pain	2.9%	2.5%
Nausea	1.7%	0.8%
Vomiting	1.7%	0%
Abdominal Discomfort	1.1%	0%
Abdominal Distension	1.1%	0%

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies was 4.6% for patients taking ACCRUFER. The most common adverse reaction leading to discontinuation of ACCRUFER in these studies was abdominal pain (1.7% of patients).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ACCRUFER

Oral Medications

There are no empirical data on avoiding drug interactions between ACCRUFER and concomitant oral medications. Concomitant use of some drugs may reduce the bioavailability of iron after administration of ACCRUFER. Separate the administration of ACCRUFER from these drugs. The duration of separation may depend on the absorption characteristics of the medication concomitantly administered, such as time to peak concentration or whether the drug is an immediate or extended release product. Monitor clinical response to ACCRUFER.

7.2 Effect of ACCRUFER on Other Drugs

Dimercaprol

Concomitant use of iron products with dimercaprol may increase the risk of nephrotoxicity. Avoid concomitant use of ACCRUFER with dimercaprol.

Oral Medications

Concomitant use of ACCRUFER may decrease the bioavailability of some drugs, including mycophenolate, ethinyl estradiol, ciprofloxacin and doxycycline *[see Clinical Pharmacology (12.3)]*. For oral drugs where reductions in bioavailability may cause clinically significant effects on its safety or efficacy, separate the administration of ACCRUFER by at least 4 hours. Monitor clinical responses to concomitant drugs as appropriate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ACCRUFER is not absorbed systemically as an intact complex following oral administration, and maternal use is not expected to result in fetal exposure to the drug *[see Clinical Pharmacology (12.3)].*

In animal reproduction studies, oral administration of ferric or ferrous compounds to gravid CD1-mice and Wistar-rats during organogenesis at doses 13 to 32 times the recommended human dose resulted in no adverse developmental outcomes. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

In animal reproduction studies, oral administration of maltol to pregnant Crl: COBS-CD (SD) BR rats during organogenesis at doses 6 times the recommended human dose resulted in no adverse developmental outcomes.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In

the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Untreated iron deficiency anemia (IDA) in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

Data

Animal Data

In embryofetal development studies in mice and rats, pregnant animals received oral doses of ferric or ferrous compounds (ferrous sulfate or ferric sodium pyrophosphate) of up to 160 mg/kg/day in mice, or up to 200 mg/kg/day in rats, during the period of organogenesis. Administration of ferric or ferrous compounds at doses 13 times (in mice) or 32 times (in rats) the recommended human dose resulted in no maternal toxicity and no adverse developmental outcomes.

In a multigeneration reproductive and developmental study in rats, pregnant animals received oral doses of maltol of 100, 200, and 400 mg/kg/day, during the period of organogenesis. Administration of maltol at doses 6 times the recommended human dose resulted in no maternal toxicity and no adverse developmental outcomes.

8.2 Lactation

Risk Summary

There are no data on the presence of ACCRUFER in human milk, the effects on the breastfed child, or the effects on milk production. ACCRUFER is not absorbed systemically as an intact complex by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to ACCRUFER.

8.4 Pediatric Use

Safety and effectiveness of ACCRUFER have not been established in pediatric patients.

8.5 Geriatric Use

Of the 295 patients in the randomized trials of ACCRUFER, 39% of patients were aged 65 and older, while 23% were aged 75 and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

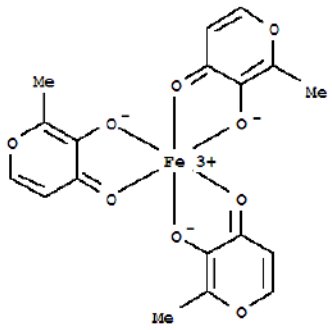
No data are available regarding overdose of ACCRUFER in patients. Acute iron ingestion of 20 mg/kg elemental iron is potentially toxic and 200- 250 mg/kg is potentially fatal. Early signs and symptoms of iron overdose may include nausea, vomiting, abdominal pain and diarrhea. In more serious cases there may be evidence of hypoperfusion, metabolic acidosis and systemic toxicity.

Dosages of ACCRUFER in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Do not administer ACCRUFER to patients with iron overload *[see Contraindications (4)]*.

11 DESCRIPTION

ACCRUFER (ferric maltol) capsules, an iron replacement product for oral administration, contain 30 mg iron and 201.5 mg maltol. Ferric maltol contains iron in a stable ferric state as a complex with a trimaltol ligand. Ferric maltol is 3-hydroxy-2-methyl-4H-pyrane-4-one iron (III) complex (3:1) and has the molecular formula $(C_6H_5O_3)_3Fe$ and a molecular mass of 431.2.

Each red capsule, printed with “30”, contains colloidal anhydrous silica, crospovidone (Type A), lactose monohydrate, magnesium stearate and sodium lauryl sulfate as inactive ingredients. In addition, the capsule shell contains FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No.6, hypromellose and titanium dioxide. The ink used for printing the marking contains ammonium hydroxide, ethanol, iron oxide black and propylene glycol.



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ACCRUFER delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin.

12.2 Pharmacodynamics

ACCRUFER has been shown to increase serum iron parameters, including ferritin and transferrin saturation (TSAT).

12.3 Pharmacokinetics

The pharmacokinetic properties of serum iron after administration of ACCRUFER was assessed in subjects with iron deficiency (with or without anemia) following a single dose and at steady state (after 1 week) of ACCRUFER 30 mg, 60 mg, or 90 mg twice daily (1 to 3 times the approved recommended dosage). Total serum iron concentrations increase in a less than dose proportional manner with increasing ACCRUFER doses.

Absorption

ACCRUFER dissociates upon uptake from the gastrointestinal tract allowing iron and maltol to be absorbed separately.

Total serum iron peak values were reached 1.5 to 3 hours after administration of ACCRUFER, and were comparable between Day 1 and Day 8.

Effect of Food
Food has been shown to decrease the bioavailability of iron after administration of ferric maltol.

Drug Interaction Studies

In vitro
Of the drugs screened for an interaction with ferric maltol in vitro at pH 1.2, 4.5 and 6.8, only mycophenolate and ethinyl estradiol showed any potential for interaction. Mycophenolate recovery was reduced by up to 16% at pH 1.2 but there was no interaction at pH 4.5; due to solubility issues data are not available for pH 6.8. Ethinyl estradiol recovery was reduced by up to 35% at pH 4.5; due to solubility issues data are not available for pH 1.2 and pH 6.8. These potential oral interactions can be avoided by spacing the administration of those drugs and ACCRUFER [*see Drug Interactions (7.2)]*.

Lisinopril, metoprolol and warfarin showed no interaction at any of the 3 pH conditions and can be taken with ACCRUFER.

No interaction with ferric maltol was observed for atorvastatin (pH 6.8), and norgestimate (pH 1.2) (data were not obtainable at the other pH conditions due to solubility issues).

In vivo
No clinical studies evaluating the drug interaction potential of ACCRUFER have been conducted.
Iron-containing preparations may decrease ciprofloxacin absorption into the bloodstream, resulting in lower serum and urine levels and reduced effectiveness.
Absorption of tetracyclines including doxycycline is reported to be impaired by iron-containing preparations.

12.6 Maltol Pharmacokinetics
Maltol is metabolized through glucuronidation (UGT1A6) and sulphation *in vitro*. Of the total maltol ingested, a mean of between 39.8% and 60% was excreted in the urine as maltol glucuronide. There was no clinically meaningful change in exposure of maltol or maltol glucuronide in subjects with non-dialysis dependent chronic kidney disease (eGFR of $\geq$15 mL/min/1.73m^2 and <60 mL/min/1.73m^2).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Ferric maltol
ACCRUFER is not absorbed systemically as an intact complex.

Carcinogenicity studies have not been conducted with ferric maltol.

Ferric maltol was mutagenic in vitro in reverse bacterial mutation (Ames) assays. Ferric maltol increased revertant frequency in the absence and presence of metabolic activation.

Fertility studies have not been conducted with ferric maltol.

Maltol

The carcinogenic potential of maltol has been evaluated in long-term animal toxicity studies in two species: CD-1 mice and Sprague-Dawley rats. Maltol was not carcinogenic in a 18-month study in mice at doses up to 400 mg/kg (approximately 5 times the human daily dose). Maltol was not carcinogenic in a 2-year study in rats at doses up to 400 mg/kg (approximately 10 times the human daily dose).

Maltol was mutagenic in vitro in reverse bacterial mutation (Ames) assays. Maltol increased revertant frequency in the absence and presence of metabolic activation. Maltol was clastogenic in vivo in a mouse micronucleus assay (increase in polychromatic erythrocytes) at intraperitoneal doses of 774 mg/kg. Absorbed maltol is rapidly conjugated with glucuronic acid. It is therefore unlikely that the mutagenic activity of maltol would be expressed under the conditions of oral human intake.

In a multi-generation animal reproduction study in male and female rats, there were no effects on mating, fertility, or early embryonic development at doses up to 400 mg/kg/day (approximately 10 times the human daily dose).

14 CLINICAL STUDIES

14.1 Patients with Inflammatory Bowel Disease (IBD)

The safety and efficacy of ACCRUFER for the treatment of iron deficiency anemia was studied in two randomized, placebo-controlled trials: AEGIS 1 (NCT01252221) and AEGIS 2 (NCT01340872). These trials enrolled 128 patients (age range 18-76 years; 45 males and 83 females) with quiescent IBD (58 patients with Ulcerative Colitis [UC] and 70 patients with Crohn's disease [CD]) and baseline Hb concentrations between 9.5 g/dL and 12 /13 g/dL for females / males and ferritin < 30 mcg/L. All patients had discontinued prior oral ferrous product treatment due to lack of efficacy or inability to tolerate oral iron replacement products. Subjects were randomized 1:1 to receive either 30 mg ACCRUFER twice daily or a matched placebo control for 12 weeks.

The major efficacy outcome was the mean difference in Hb concentration from baseline to week 12 between ACCRUFER and placebo. The Least Square [LS] mean difference from baseline was 2.18 g/dL (p<0.0001)(see Table 2).

Table 2. Summary of Hemoglobin Concentration (g/dL) and Change From Baseline to Week 12 AEGIS 1 & 2 - Analysis Using Multiple Imputation - Full Analysis Set Population

Visit (Week) Statistic	**ACCRUFER (N = 64)**	**Placebo (N =64)**	
Baseline			
Mean (SD)	11.0 (1.03)	11.10 (0.85)	
Mean change from baseline to Week 12			
LS Mean (SE)	2.25 (0.12)	0.06 (0.13)	
	Difference in Change From Baseline		
Treatment Comparison	**LSM Difference (SE) ACCRUFER – Placebo)**	**1-sided lower 97.5%CI**	**p-value**
ACCRUFER versus placebo	2.18 (0.19)	(1.81)	<0.0001

Note: Multiple imputation was based on treatment, gender, disease [UC or CD], and Hb concentration at baseline, Week 4, and 8. For each imputed dataset, the change from baseline to Week 12 was analyzed using an ANCOVA model with treatment as the factor and gender, disease, baseline Hb concentration as covariates.

The LS mean difference in change from baseline Hb to Week 4 and 8 between ACCRUFER and placebo were 1.04 g/dl and 1.73 g/dl, respectively.

The mean ferritin (mcg/L) levels in ACCRUFER subjects at baseline were 8.6 mcg/L [SD 6.77]) and the mean ferritin (mcg/L) levels at Week 12 were 26.0 mcg/L [SD 30.57] with a mean overall improvement of 17.3 mcg/L.

Following completion of the 12-week placebo-controlled phase of the studies, eligible patients transitioned to ACCRUFER 30 mg twice daily open-label treatment for an additional 52 weeks.

During the open-label phase with ACCRUFER, the mean change in Hb concentration from baseline to Week 64 was 3.1 g/dL [SD 1.46 g/dL, n = 35] and the ferritin value demonstrated a mean of 68.9 mcg/L [SD 96.24] at 64 weeks, with a mean overall improvement of 60.4 mcg/L.

14.2 Patients with Chronic Kidney Disease (CKD)

The safety and efficacy of ACCRUFER for the treatment of iron deficiency anemia was studied in AEGIS 3 (NCT02968368), a trial that enrolled 167 patients (mean age 67.4 years, range 30-90 years; 50 males and 117 females) with non-dialysis dependent chronic kidney disease (CKD) and baseline hemoglobin (Hb) concentrations between 8g/dL and 11 g/dL and ferritin < 250 mcg/L with a Transferrin saturation (TSAT) <25% or ferritin < 500 mcg/L with a TSAT <15%. ACCRUFER was administered at a dose of 30 mg twice daily. Subjects were randomized 2:1 to receive either 30 mg ACCRUFER twice daily or a matched placebo control for 16 weeks.

The major efficacy outcome was the mean difference in Hb concentration from baseline to Week 16 between ACCRUFER and placebo. The LS mean difference was 0.52 g/dL (p= 0.0149) (see Table 3).

Table 3. Summary of Hemoglobin Concentration (g/dL) and Change From Baseline to Week 16 - Analysis Using Multiple Imputation – Intent-to-Treat Population

Visit (Week) **Statistic**	**ACCRUFER** **(N = 111)**	**Placebo** **(N = 56)**	
Baseline			
Mean (SD)	10.06 (0.77)	10.03 (0.82)	
Mean change from baseline to Week 16			
LS Mean (SE)	0.50 (0.12)	-0.02 (0.16)	
	Difference in Change From Baseline		
Treatment Comparison	**LSM Difference (SE)** **ACCRUFER – Placebo**	**95% CI**	**p-value**
ACCRUFER versus placebo	0.52 (0.21)	(0.10, 0.93)	0.0149

Note: Multiple imputation was based on treatment, gender, eGFR at baseline, and Hb concentration at baseline, Week 4 and 8. For each imputed dataset, the change from baseline to Week 16 was analyzed using an ANCOVA model with treatment as the factor and baseline Hb concentration, baseline eGFR as covariates.

The LS mean difference in change from baseline Hb to Week 4 and 8 between ACCRUFER and placebo were 0.13 g/dl and 0.46 g/dl, respectively.

The mean change in ferritin concentration from baseline to Week 16 was 49.3 mcg/L for the ACCRUFER group and 6.3 mcg/L for the placebo group. The mean difference for ACCRUFER versus placebo was 43.0 mcg/L.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ACCRUFER (ferric maltol) 30 mg iron capsules are supplied as 60 capsules in HDPE bottles with a child-proof polypropylene push-lock.

1 Bottle of 60-count 30 mg ferric iron capsules (NDC 73059-001-60).

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dosing Recommendations

Inform patients to take ACCRUFER as directed on an empty stomach, at least 1 hour before or 2 hours after meals. Instruct patients on concomitant medications that should be dosed apart from ACCRUFER *[see Dosage and Administration (2.1) and Drug Interactions (7.2)]*.

Adverse Reactions

Advise patients that ACCRUFER may cause, flatulence, diarrhea, constipation, discolored feces, abdominal pain, nausea, vomiting or abdominal bloating or discomfort. Advise patients to report severe or persistent gastrointestinal symptoms or any allergic reactions to their physician *[see Adverse Reactions (6.1)].*

Increased Risk of IBD Flare

Advise patients that they should not use ACCRUFER if they are experiencing an IBD flare.

Iron Overload and Risk of Accidental Overdose in Children

Inform patients to keep this product out of reach of children as accidental over dose of iron products is a leading cause of fatal poisonings in children. In case of accidental overdose, advise them to call a doctor or poison control center immediately *[see Warnings and Precautions (5.2)]*.

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Patient Information
ACCRUFER® (ak-roo-fer)
(ferric maltol)
capsules

What is ACCRUFER?

ACCRUFER is a prescription medicine used in adults to treat low iron stores in your body.

It is not known if ACCRUFER is safe and effective for use in children.

Do not take ACCRUFER if you:

- are allergic to ferric maltol or any of the ingredients in ACCRUFER. See the end of this leafelet for a complete list of ingredients in ACCRUFER.
- have any illness that causes you to store too much iron in your body or if you have a problem with how your body uses iron.
- are receiving repeated blood transfusions.

Before taking ACCRUFER, tell your healthcare provider about all your medical conditions, including if you:

- have inflammatory bowel disease (IBD).
- are pregnant or plan to become pregnant. It is not known if ACCRUFER will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ACCRUFER passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby during treatment with ACCRUFER.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking ACCRUFER with certain other medicines may affect each other causing serious side effects.

Some medicines may need to be taken at least 4 hours before or 4 hours after you have taken your ACCRUFER dose. Ask your healthcare provider for a list of these medicines if you are not sure if you take one of these medicines.

Especially tell your healthcare provider if you take:

- dimercaprol
- other oral iron tablets or health supplements containing iron

Ask your healthcare provider if you are not sure if you take one of these medicines.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ACCRUFER?

- Take ACCRUFER exactly as your healthcare provider tells you to.
- Take ACCRUFER 2 times a day on an empty stomach 1 hour before or 2 hours after meals.
- Swallow ACCRUFER capsules whole. **Do not** open, break, or chew ACCRUFER capsules.
- In case of accidental overdose, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ACCRUFER?

ACCRUFER may cause serious side effects, including:

- **Increased risk of inflammatory bowel disease (IBD) flare.** You should avoid taking ACCRUFER if you have inflammatory bowel disease (IBD) and are experiencing a flare.
- **Too much iron stored in your body (iron overload).** Your healthcare provider should check the iron level in your blood before you start and during treatment with ACCRUFER.
- **Risk of overdose in children due to accidental swallowing.** Accidental overdose of iron-containing products is a leading cause of death from poisoning in children under 6. Keep ACCRUFER in a safe place and out of the reach of children.

The most common side effects of ACCRUFER include:

- gas
- constipation
- diarrhea
- discolored stools

- stomach pain
- nausea or vomiting
- stomach area discomfort or bloating

These are not all the possible side effects of ACCRUFER.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ACCRUFER?

- Store ACCRUFER at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ACCRUFER and all medicines out of reach of children.

General information about the safe and effective use of ACCRUFER.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ACCRUFER for a condition for which it was not prescribed. Do not give ACCRUFER to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ACCRUFER that is written for health professionals.

What are the ingredients in ACCRUFER?

Active ingredient: ferric maltol

Inactive ingredients:

Capsule: colloidal anhydrous silica, crospovidone (Type A), lactose monohydrate, magnesium stearate, sodium lauryl sulfate

Capsule Shell: FD&C Blue No. 1 FD&C Red No. 40, FD&C Yellow 6, hypromellose, titanium dioxide.

Ink: ammonium hydroxide, ethanol, iron oxide black, propylene glycol

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US Patents 7459569, 9248148, 9802973, 10179120

This Patient Information has been approved by the U.S. Food and Drug Adminstration. Issued: February 2022