

IRON THEY'LL ACTUALLY TAKE¹

ACCRUFer[®] (ferric maltol) has a unique “maltol shield” that protects the iron as it passes through the stomach, resulting in unprecedented GI tolerability and clinically proven efficacy.^{2,3}



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:


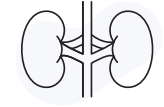
- Hypersensitivity to ACCRUFer or any of its inactive components
- Hemochromatosis and other iron overload syndromes
- Receiving repeated blood transfusions as this may result in iron overload

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

PATIENTS WITH ID/IDA NEED TOLERABLE AND EFFECTIVE TREATMENT

In the United States, about 10 million people have iron deficiency (ID) and about 5 million have iron deficiency anemia (IDA).⁴

Prevalence is highest in women of childbearing age and patients with inflammatory conditions.⁵

 <p>Women's health</p> <ul style="list-style-type: none"> • Menorrhagia • Pregnancy • Uterine Fibroids 	 <p>Inflammatory bowel disease</p> <ul style="list-style-type: none"> • Crohn's disease • Ulcerative colitis 	 <p>Chronic kidney disease</p>
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Traditional oral iron treatments, such as ferrous salts (Fe²⁺), often cause GI side effects because they dissociate in the stomach.

- When ferrous salts dissociate in the stomach, they can bind together, creating clumps that are hard to absorb. 90% of Fe²⁺ in ferrous salts goes unabsorbed.⁷
- Unabsorbed Fe²⁺ oxidizes, which can generate reactive oxygen species (ROS).^{3,7,11}
- ROS can cause irritation and damage when they reach the intestinal lining, contributing to GI discomfort.^{3,7,11}

Additionally, free iron in the colon can have adverse impacts on the gut microbiome, adding to the inflammation with which IBD patients are already dealing.⁸


Up to **60%** of patients will **discontinue treatment** with ferrous salts because of adverse reactions.⁶

More than two-thirds of people taking traditional oral iron report GI issues, such as:^{9,10}


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

WHY ACCRUFER?

ACCRUFER is an FDA-approved treatment that delivers a low dose of elemental iron that can reverse IDA while minimizing risk for unmanageable GI side effects.²



Designed with a “maltol shield”
 Uniquely formulated with a “maltol shield” that **protects the iron as it passes through the stomach**, reducing the likelihood of reactive oxygen species formation, which **minimizes GI side effects**.^{2,12,14}




Unprecedented tolerability
 In clinical studies, 4.6% of patients taking ACCRUFER (n=175) discontinued treatment due to adverse gastrointestinal reactions, compared with 2.5% of patients taking a placebo (n=120).²



Established safety and efficacy
 FDA approval was achieved based on three pivotal studies in patients with ID/IDA associated with chronic inflammation and malabsorption, resulting in **significant improvement across iron indices**, including hemoglobin, ferritin, and TSAT.^{*2,11,12}

*Not to be used by patients with an active IBD flare



Committed to affordability
 Eligible patients may **pay as little as \$0** for ACCRUFER.*

* Restrictions apply.

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.

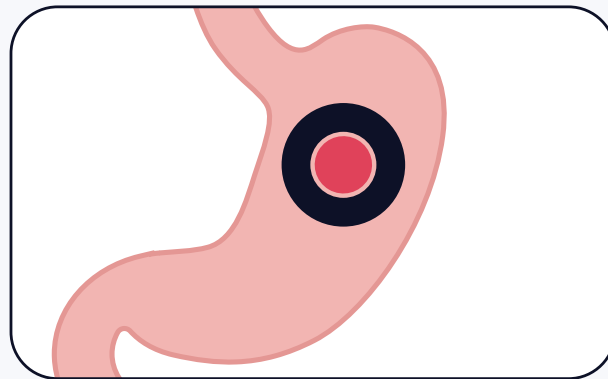
Please see Important Safety Information throughout and accompanying full Prescribing Information.

UNIQUELY FORMULATED WITH A “MALTOL SHIELD”

ACCRUFer is a stable complex of ferric iron (Fe³⁺) and maltol, a naturally occurring sugar derivative.^{2,12} Unlike iron salts, this iron-sugar derivative complex stays intact in the stomach, dissociating when it reaches the duodenum for optimal iron absorption.²

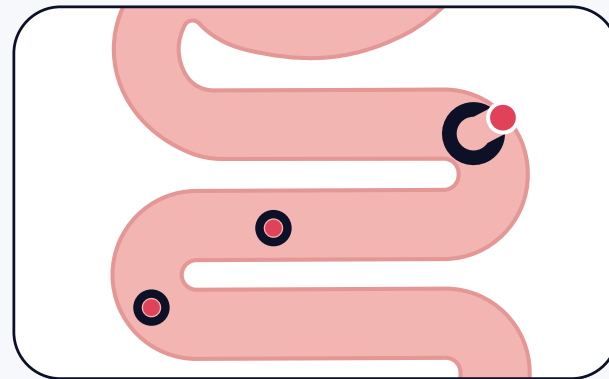
ACCRUFer in Action

Tightly bound in the stomach



The “maltol shield” protects iron from the stomach, remaining tightly bound as it passes through.

Dissociates upon uptake in the duodenum



Iron remains bioavailable, chelated, and ready to replenish iron stores. Excess iron is excreted in the stool.



Why the “maltol shield” matters:¹²

- It reduces the likelihood of reactive oxygen species (ROS) formation, **minimizing the risk** for GI side effects and irritation or damage to the intestinal lining.
- Since the iron and maltol remain chelated until absorption, there is **less free iron** in the gut, lessening the risk for added bowel inflammation.

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 Prescribing Information.

UNPRECEDENTED TOLERABILITY AND ESTABLISHED SAFETY

In clinical studies, GI adverse reactions were mild to moderate in nature, and less than 5% of patients reported individual GI adverse reactions.²

Pooled Results from AEGIS IBD and AEGIS CKD

Adverse reactions reported by ≥1% of patients treated with ACCRUFer during the double-blind period of placebo-controlled studies²

Gastrointestinal Adverse Reactions	ACCRUFer (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 distension	1.1%	0%

Excluding open-label extension period

In clinical trials, **4.6%** of patients (n=175) discontinued ACCRUFer because of GI adverse reactions compared to 2.5% of patients (n=120) on placebo.²

Neither short- nor long-term treatment led to iron overload.^{1,11,12}

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.

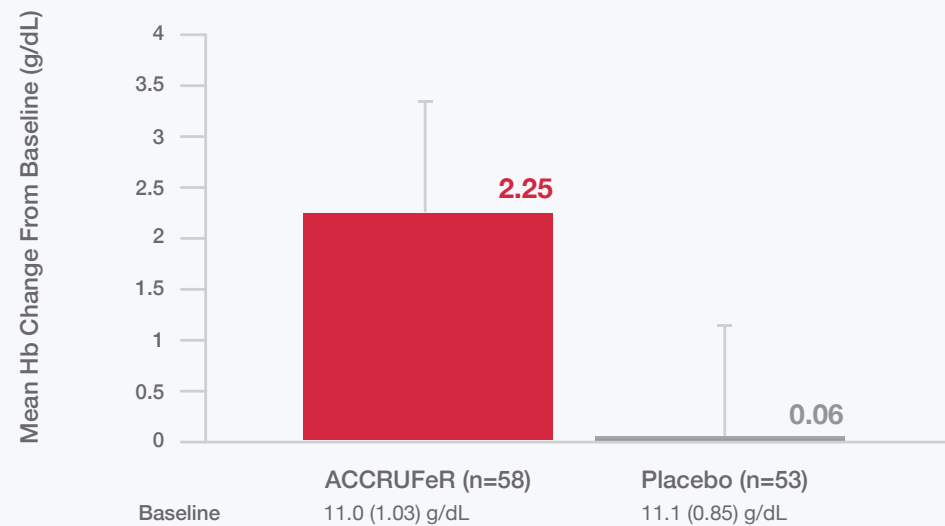
To report adverse events, please contact Shield Therapeutics at 1-888-963-6267. You may also contact the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

SIGNIFICANT AND RAPID IMPROVEMENTS IN HEMOGLOBIN IN ADULTS WITH IBD

ACCRUFER established safety and efficacy in patients with Crohn's disease and ulcerative colitis in two 12-week, phase 3A, randomized and placebo-controlled pivotal trials with a 52-week open label extension phase in patients that had previously failed treatment with oral ferrous products.^{1,2,11}

Primary Endpoint: LS Mean (SE) Hb Concentration from Baseline to Week 12

One-sided 97.5% CI, 1.81; P<0.0001 based on ANCOVA



2.25 (0.12) g/dL
 LS mean (SE) improvement in Hb in the ACCRUFER group.²

Statistical significance was achieved as early as **Week 4**.

At Week 12 **78%** of patients (n=64) taking ACCRUFER saw a **≥1 g/dL increase in Hb** compared to 11% on placebo.^{1,11}

**According to responder analysis*

Secondary Endpoints:

Mean (SD) Increase; ACCRUFER increased ferritin levels and TSAT.

	ACCRUFER (n=64)	Placebo (n=64)
Ferritin (mcg/L)	17.3 (28.30)	1.2 (7.85)
TSAT, %	+18% (20.2)	-0.4% (7.8)

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 Prescribing Information.

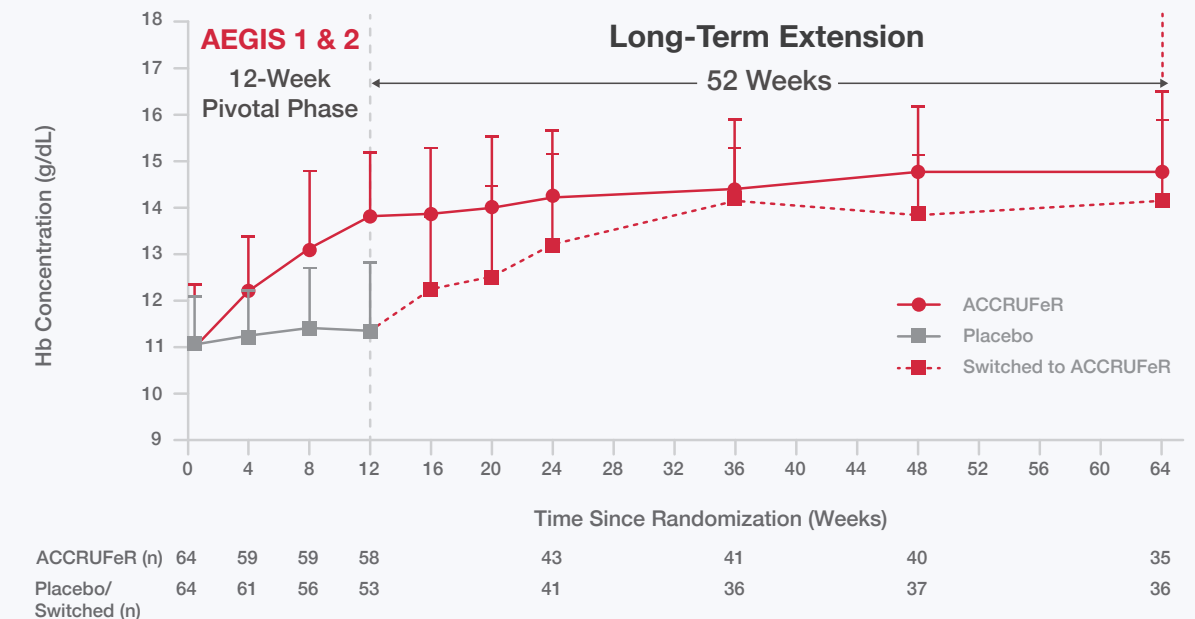
IMPROVEMENTS IN Hb WERE MAINTAINED UP TO 64 WEEKS

At Week 12, patients on placebo switched to ACCRUFER, and patients already on treatment continued for an additional 52 weeks.^{1,2}

Mean Improvement in Hb from Baseline to Week 64

Hb in patients on ACCRUFER	Hb in patients on placebo who switched after Week 12
3.07 (±1.46) g/dL	2.19 (±1.61) g/dL

Absolute Hb Concentrations from Baseline to Week 64



At Week 64 **86%** The cumulative proportion of patients (n=111) who **maintained normal Hb** was 86.1%.¹

**According to responder analysis*

WARNINGS AND PRECAUTIONS

INCREASED RISK OF INFLAMMATORY BOWEL DISEASE (IBD) FLARE

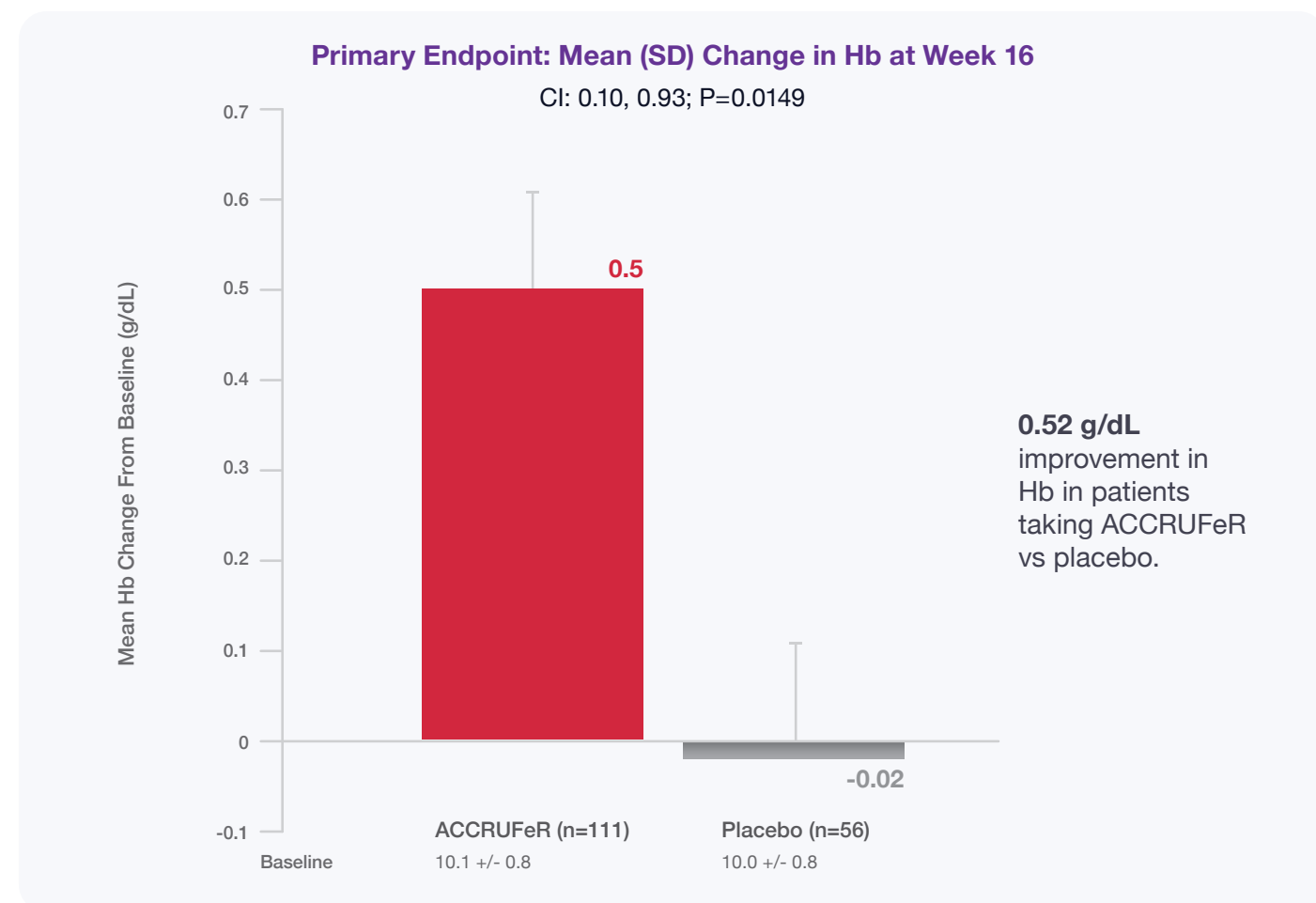
Avoid use of ACCRUFER in patients with an active IBD flare, as there is potential risk of increased inflammation in the gastrointestinal tract.

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.

SIGNIFICANT IMPROVEMENTS IN HEMOGLOBIN IN ADULTS WITH CKD^{2,12}

ACCRUFer established safety and efficacy in patients with stage 3 or 4 chronic kidney disease (CKD), **excluding those on erythropoiesis-stimulating agents**, in a 16-week, phase 3A, randomized and placebo-controlled pivotal trial with a 36-week open label extension phase.



Secondary Endpoints:
 Mean change from baseline to Week 16

	ACCRUFer (n=111)	Placebo (n=56)	Mean difference
Ferritin (mcg/L)	49.3	6.3	43.0 mcg/L P<0.001
TSAT* (LS Mean, SE)	3.8 (0.6)	-0.9 (0.9)	4.6 (1.1) P<.001

*Reflects percentage change

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.

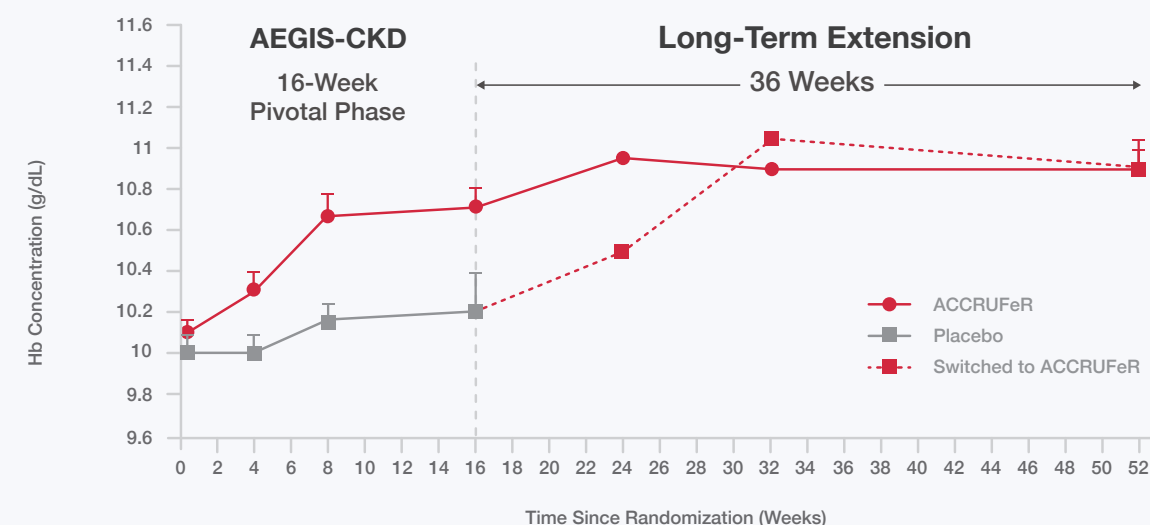
INCREASED Hb CONCENTRATIONS WERE MAINTAINED OVER 52 WEEKS

At Week 16, patients on placebo switched to ACCRUFer, and patients already on treatment continued for an additional 36 weeks.^{2,12} Increases in Hb for patients taking ACCRUFer at Weeks 4, 8, and 16 were consistent with changes seen in the AEGIS-IBD studies.^{2,13}

Mean Improvement in Hb from Baseline to Week 52

Hb in patients on ACCRUFer	Hb in patients on placebo who switched after Week 16
0.7 (±1.7) g/dL	0.5 (±1.4) g/dL

Absolute (SE) Hb Concentrations in Patients Over 52 Weeks



	0	4	8	16	24	32	40	52
ACCRUFer (n)	111	103	94	88	77	68	60	67
Placebo/ Switched (n)	56	52	46	40	32	29	26	30

No patients treated with ACCRUFer in either long-term study required IV iron intervention^{1,11,12}

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.

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.

PATIENTS TAKE **ONE 30-MG, GLUTEN-FREE CAPSULE BID²**

Treatment considerations²

- Advise patients to take ACCRUFer 1 hour before or 2 hours after a meal.
- Treatment duration depends on deficiency severity; at least 12 weeks of treatment is typically needed.
- Treatment with ACCRUFer should be continued until ferritin levels are within normal ranges.
- Stool softener or other supplements, like vitamin C, are not required.

97%

median overall treatment compliance rate was seen across a 12-week and 52-week open label extension.¹



We're committed to making ACCRUFer affordable through **BlinkRx** pharmacy

Patients with commercial insurance may pay \$0 or \$25

If a PA is required

- and approved by insurance, your patient will have a \$0 copay.
- but not approved by insurance, your patient will have a \$25 copay.
- but not submitted, your patient will have a \$115 copay.

Patients with Medicare Part D are automatically eligible for a \$25 cash price.

Patients with Medicaid Coverage and copays vary by state.

START YOUR PATIENTS ON **ACCRUFer**

BLINKRx PHARMACY



Patients with Commercial Insurance and Medicare May Pay No More Than \$25



A Free 30-day Supply of ACCRUFer
For patients with commercial insurance



Prior Authorization Support



Free, Fast Delivery

BLINKRx
BENEFITS

HOW TO GET STARTED

- 1** E-prescribe ACCRUFer® by selecting **BlinkRx** (**Boise, Idaho 83705**) in your EMR dropdown (**NCPDP number: 1310488**).
- 2** Expect a call from **BlinkRx** to get prior authorization approved, if needed.
- 3** Tell your patients that **BlinkRx** will be calling or texting them. They must respond to receive their prescription.

QUESTIONS?

Contact information

Phone: (844) 926-2480

Fax: (866) 585-4631

Support hours:

Monday – Friday 8 a.m. – 9 p.m. ET

Saturdays 9 a.m. – 5 p.m. ET



GIVE THEIR STOMACH A BREAK



Prescribe an iron they'll actually take.¹

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

About AEGIS IBD

STUDY DESCRIPTION The study enrolled 128 IBD patients (58 ulcerative colitis, 70 Crohn's disease) with IDA across 2 studies. Hb concentrations were between 9.5 g/dL and 12/13 g/dL for females/males and ferritin <30 mcg/L. 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. **STUDY ENDPOINTS** Primary endpoint: Mean difference in Hb concentration from baseline to Week 12 between ACCRUFer and placebo. Secondary endpoints: Changes in Hb concentration from baseline to Weeks 4 and 8, serum ferritin concentration, and TSAT. **BASELINE CHARACTERISTICS** Mean age: 38.5 (placebo) to 40.1 (ACCRUFer) years. Gender and ethnicity: 45 males and 83 females; 122 white and 6 others.

About AEGIS CKD

STUDY DESCRIPTION The study included 167 stage 3 or 4 CKD patients with IDA that were randomized 2:1 (ACCRUFer to placebo). **STUDY ENDPOINTS** Primary endpoint: The mean difference in Hb concentration from baseline to Week 16 between ACCRUFer and placebo. Secondary endpoints: Proportions of patients with Hb increases of at least 1 g/dL and at least 2 g/dL at Week 16; the proportion of patients achieving a Hb concentration of at least 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. **BASELINE CHARACTERISTICS** Mean age: 65.2 (placebo) to 68.5 (ACCRUFer) years, range 30-90 years. Gender and ethnicity: 50 males and 117 females; 123 White, 35 African American, and 9 other.

REFERENCES

1. 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 2. ACCRUFer® full prescribing information. Shield Therapeutics, 2023. 3. 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. 4. Miller JL. Iron deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med.* 2013;3(7):a011866. doi:10.1101/cshperspect.a011866. 5. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anemia revisited. *J Intern Med.* 2020;287(2):153-170. doi:10.1111/joim.13004 6. 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 7. Howaldt S, Domènech E, Martínez 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. 8. Ems T, et al. Biochemistry, Iron Absorption. *StatPearls* [Internet]; 2021. 9. DeLoughery TG. Safety of oral and intravenous iron. *Acta Haematologica.* 2019;142(1):8-12. doi:10.1159/000496966. 10. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrus sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One.* 2015;10(2):e0117383. doi:10.1371/journal.pone.0117383. 11. 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.00000000000003146. 12. 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.e1. doi:10.1053/j.ajkd.2021.03.020. 13. Data on file. Shield Therapeutics Inc. 2022. 14. European Medicines Agency. Assessment report: Feraccru. https://www.ema.europa.eu/en/documents/variation-report/feraccru-h-c-2733-ii-0010-epar-assessment-report-variation_en.pdf Published 2018. Accessed February 2024.

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: 10/2023

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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

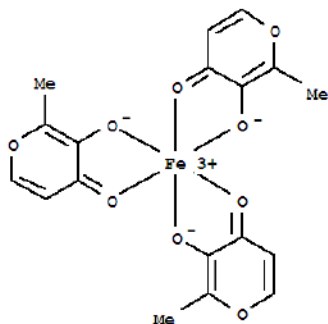
No data are available regarding overdose of ACCRUFER in patients. Acute iron ingestion of 20 mg/kg elemental iron is potentially toxic and 200- 250 mg/kg is potentially fatal. Early signs and symptoms of iron overdose may include nausea, vomiting, abdominal pain and diarrhea. In more serious cases there 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-pyran-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 ≥ 15 mL/min/1.73m² and < 60 mL/min/1.73m²).

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)	
Treatment Comparison	Difference in Change From Baseline		
	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)*].

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 leaflet 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
- stomach pain
- stomach area discomfort or bloating
- diarrhea
- discolored stools
- nausea or vomiting

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

Distributed by Shield Therapeutics Inc, Suite 200, 100 Worcester Street, Wellesley Hills, MA, 02481

US Patents 7459569, 9248148, 9802973, 10179120

This Patient Information has been approved by the U.S. Food and Drug Administration.

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