LIFE IS FULL OF IRONY

You don't need it in your iron

Most oral iron that's made to make you feel better can end up making you feel worse. ACCRUFeR is the FDA-approved oral iron that takes the irony out of oral iron—it's designed to do what it's actually supposed to do.

ACCRUFeR®
(ferric maltol) *30 mg capsules*

The Un-ironic Iron

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.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

Let’s talk about iron deficiency and iron-deficiency anemia

It’s important to understand why iron is essential to your body

Iron has a crucial function

Iron is an essential element that your body needs. It **helps your body make hemoglobin**, a protein in your blood that carries oxygen from your lungs throughout your body.

So, iron deficiency is a big deal

Iron-deficiency (ID) means there's too little iron in the body, which **means you're not getting the oxygen you need** throughout your body. It happens when the body either does not absorb enough iron or loses iron, most commonly through blood loss.

And if your ID progresses to IDA, it can cause more serious problems

Iron deficiency anemia (IDA) means you **don't have enough red blood cells to carry oxygen** inside your body. Anemia can be temporary or long-term, and it can range from mild to severe.

If your IDA goes undiagnosed or untreated, you could experience more serious problems including:

- Restless legs syndrome
- Heart problems
- Pregnancy complications that could affect you and your baby:
  - Small for gestational age, increased risk of preterm birth and/or C-section, low birth weight, NICU admission, and developing ID in first year of life

IDA can also worsen other chronic conditions you may have or make your medications less effective.

You might not realize it's ID/IDA at first

Symptoms of ID and IDA can start as mild and worsen over time

- Feeling tired
- Headaches
- Feeling dizzy
- Pale skin
- Cold hands and feet
- Tingling/numbness in hands and/or feet
- Shortness of breath
- Chest pain
- Fast heartbeat
- Trouble breathing during exercise
- Unusual cravings for nonnutritive substances such as ice, dirt, or starch

Your doctor may ask you to have blood tests measuring your hemoglobin, ferritin, and TSAT

- **Hemoglobin** levels measure the amount of hemoglobin, a protein made of iron that helps transport oxygen in the blood throughout the body
- **Ferritin** levels help your doctor understand how much iron your body stores
- **TSAT (transferrin saturation)** levels measure how much of your stored iron is available to make new red blood cells

Decreased ferritin and TSAT levels are among the first signs of ID and IDA.

How to tell if you are at risk of ID or IDA

Some health conditions can increase your risk of ID or IDA, including:

- **Women's health conditions:** heavy menstruation, pregnancy, childbirth, peri-/postmenopause, uterine fibroids

Up to 75% of women may develop IDA in their lifetime

- **Diseases:** inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), chronic kidney disease, heart failure, cancer
- **Nutritional deficits:** restrictive diets, poor nutrition, inability to absorb iron from food
- **Blood loss:** surgery, injury, frequent blood donation

IMPORTANT SAFETY INFORMATION

Do not take ACCRUFeR if you are allergic to ferric maltol or any of the 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.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

The treatment for ID/IDA has been the same for years

Most people start with oral iron supplements or over-the-counter medications, which:

- Are not approved by the FDA
- Do not require clinical studies
- Can be prescribed or purchased over-the-counter

When people cannot tolerate oral iron or need a significant increase in iron in a short period of time, IV iron may be used. IV iron is given in a professional setting, like a hospital or clinic.

TRADITIONAL ORAL IRON IS WIDELY AVAILABLE, BUT THERE'S A CATCH

IMPORTANT SAFETY INFORMATION

Before you take ACCRUFeR, tell your doctor 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; talk to your doctor if you are pregnant or plan to become pregnant); are breastfeeding or plan to breastfeed (it is not known if ACCRUFeR passes into your breast milk; talk to your doctor about the best way to feed your baby if you take ACCRUFeR).

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

There's an irony in oral iron

Traditional oral iron just makes most people feel worse

This is because when traditional oral irons break down in the stomach, most of the iron can't be absorbed. The leftover iron creates molecules that can irritate your digestive system. When a treatment is just making you feel worse, it can be hard to keep taking it.

Up to 70% of people experience gastrointestinal side effects, including:

- Heartburn
- Nausea
- Diarrhea
- Discolored stool
- Gas
- Constipation

UP TO 3 IN 5 PEOPLE STOP TAKING THEIR IRON TREATMENT DUE TO SIDE EFFECTS

IMPORTANT SAFETY INFORMATION

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

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

It’s time for iron without the irony

ACCRUFeR is an effective treatment that your body can tolerate

ACCRUFeR is the only FDA-approved oral iron for adults with low iron stores, regardless of underlying condition

ACCRUFeR is not a supplement. It is an oral prescription medicine that was studied in clinical trials and was thoroughly reviewed by the FDA.

ACCRUFeR is uniquely designed

ACCRUFeR is different because it contains a sugar-like substance called maltol. The maltol shields the iron and prevents it from reacting in the stomach. This leads to demonstrated absorption in the intestines.

That, in turn, reduces the risk of unpleasant gastrointestinal side effects such as constipation or nausea.

THE UN-IRONIC IRON THAT MAKES YOU FEEL BETTER, NOT WORSE

IMPORTANT SAFETY INFORMATION

ACCRUFeR and certain other medicines may interact, which could potentially cause serious side effects. Some medicines may need to be taken at least 4 hours before or 4 hours after you have taken ACCRUFeR. Ask your healthcare provider for a list of these medicines if you are not sure if you take one of these medicines.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

ACCRUFeR®
(ferric maltol) *30 mg capsules*

There are clinical studies to back it up

ACCRUFeR is an effective low-dose treatment for ID and IDA

ACCRUFeR was studied in multiple clinical trials that measured indicators of iron levels such as hemoglobin, TSAT, and ferritin over the course of a year.

ACCRUFeR rapidly returned hemoglobin levels to normal

By week 4

one-third of people taking ACCRUFeR had normal hemoglobin levels

By week 12

three-quarters of people taking ACCRUFeR had normal hemoglobin levels

ACCRUFeR also improved other markers (such as ferritin and TSAT) that show iron stores are being built up over the course of the study.

> PEOPLE WHO TOOK ACCRUFeR OVER THE COURSE OF A YEAR SUSTAINED HEMOGLOBIN LEVELS

IMPORTANT SAFETY INFORMATION

Especially tell your healthcare provider if you take:

- Dimercaprol

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

Results made possible by a treatment you can tolerate

The most common GI side effect was gas, and it was experienced by <5% of patients

Other most common side effects:

- Discolored stool
- Stomach area discomfort or bloating
- Stomach pain
- Nausea, vomiting
- Diarrhea
- Constipation

4.6%

Only 4.6% of people taking ACCRUFeR stopped treatment due to adverse reactions*

*Excluding the open-label extension period.

IMPORTANT SAFETY INFORMATION

- 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.

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 IBD and are experiencing a flare

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

ACCRUFeR®
(ferric maltol) *30 mg capsules*

We've made treatment easy with ACCRUFeR

Take one 30-mg capsule of ACCRUFeR twice a day on an empty stomach.

Take ACCRUFeR exactly as your doctor tells you.

Supplements such as stool softeners are not required when taking ACCRUFeR.

Tips for taking ACCRUFeR

- Take ACCRUFeR 1 hour before or 2 hours after a meal
- Try taking your morning dose as soon as you wake up
- Make iron part of your evening post-dinner routine

Talk to your doctor

Taking ACCRUFeR with certain other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements, may affect how each medicine works, causing serious side effects.

Treatment considerations

How long should you take ACCRUFeR?

- Everyone is different, but most people may need to take ACCRUFeR for at least 12 weeks to build up iron stores
- You should keep taking ACCRUFeR for as long as your doctor tells you to. It is safe for long-term use

You should not take ACCRUFeR if you:

- Are allergic to ferric maltol or any of the ingredients in ACCRUFeR. See the end of the Prescribing Information 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 getting repeated blood transfusions
- Are experiencing an active IBD flare

IMPORTANT SAFETY INFORMATION

What are the possible side effects of ACCRUFeR?

- **Too much iron stored in your body (iron overload).** Your healthcare provider should check the iron level in your blood before you start treatment with ACCRUFeR

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

ACCRUFeR®
(ferric maltol) *30 mg capsules*

Getting ACCRUFeR is simple and affordable

Shield's partnership with BlinkRx, an e-pharmacy, helps ensure you can access the iron-replacement therapy you need.

BlinkRx can even help you save

- If you have commercial insurance, you pay as little as $0 for a first fill and up to $25 for subsequent refills
- If you have Medicare Part D, you will be automatically eligible for a $25 cash price
- If you have Medicaid, coverage varies by state

Need help with BlinkRx?

1 (844) 926-2480

Support Hours

Monday - Friday 8am - 9pm ET

Saturdays 9pm - 5pm ET

OPT IN TO AUTOMATIC REFILLS AND NEVER MISS A DOSE

IMPORTANT SAFETY INFORMATION

What are the possible side effects of 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

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

Delivered to your door in 3 easy steps

STEP 1: BLINKRx WILL CONTACT YOU

Once your doctor sends your prescription to BlinkRx, they will call or text you with a confidential link with your prescription details.

You must respond and confirm with BlinkRx to receive your prescription.

STEP 2: CHECK OUT ONLINE

BlinkRx verifies your insurance to apply all eligible savings to your copay. They'll let you know when it's time to check out so you can pay online and confirm your delivery address.

STEP 3: DELIVER TO YOUR DOOR

Delivery is always free.

ACCRUFeR®
(ferric maltol) 30 mg capsules

We've taken care of the irony

TIME TO TAKE CARE OF YOU

ACCRUFeR is The Un-ironic Iron that hits all the marks:

- The only FDA-approved oral iron for adults with low iron stores, regardless of underlying condition
- Proven safety and unprecedented tolerability in clinical trials
- Unique design and demonstrated absorption
- Pay no more than $25 with free delivery to your home in just a few clicks*

*For eligible patients.

Scan QR code to learn more

Talk to your doctor about how ACCRUFeR could work for you.

IMPORTANT SAFETY INFORMATION

The most common side effects of ACCRUFeR include gas, diarrhea, constipation, discolored stools, stomach pain, nausea, vomiting, and stomach area discomfort or bloating. These are not all the possible side effects of ACCRUFeR. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information about ACCRUFeR.

ACC-US-00135 2/2023

shield therapeutics

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

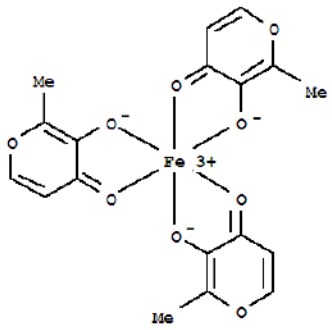
No data are available regarding overdose of ACCRUFER in patients. Acute iron ingestion of 20 mg/kg elemental iron is potentially toxic and 200- 250 mg/kg is potentially fatal. Early signs and symptoms of iron overdose may include nausea, vomiting, abdominal pain and diarrhea. In more serious cases there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

Distributed by Shield Therapeutics Inc, 9020 Capital of Texas Highway North, Austin, TX, 78759

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

Distributed by Shield Therapeutics Inc, 9020 Capital of Texas Highway North, Austin, TX, 78759

US Patents 7459569, 9248148, 9802973, 10179120

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