

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 TX (UK) Ltd. 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: 10/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Inflammatory Bowel Disease (IBD) Flare

5.2 Iron Overload

5.3 Risk of Overdosage in Children Due to Accidental Ingestion

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ACCRUFER

7.2 Effect of ACCRUFER on Other Drugs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.6 Maltol Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Patients with Inflammatory Bowel Disease (IBD)

14.2 Patients with Chronic Kidney Disease (CKD)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

* 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

The following information is based upon published case reports and clinical studies that could not be confirmed by an adequately controlled study with ACCRUFER, but still warrant consideration given the potential risks involved with iron products.

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

There are no empirical data on avoiding drug interactions between ACCRUFER and concomitant oral medications. Concomitant use of ACCRUFER may decrease the bioavailability of some drugs. 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 CrI: 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

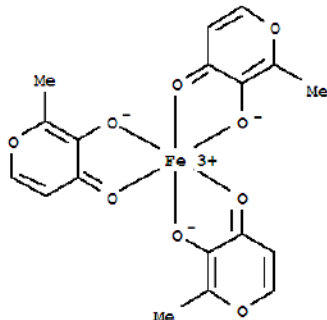
No data are available regarding overdose of ACCRUFER in patients. Acute iron ingestion of 20 mg/kg elemental iron is potentially toxic and 200- 250 mg/kg is potentially fatal. Early signs and symptoms of iron overdose may include nausea, vomiting, abdominal pain and diarrhea. In more serious cases there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

No clinical studies evaluating the drug interaction potential of ACCRUFER have been conducted.

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)	
	Difference in Change From Baseline		
	LSM Difference (SE)	1-sided lower 97.5%CI	p-value
Treatment Comparison	ACCRUFER – Placebo)		
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 6.6 mcg/L for the placebo group. The mean difference for ACCRUFER versus placebo was 42.7 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)*].