126243

- Soluble non-ionic iron preparation -

Ferrocyte® 50mg TABLETS

<Sodium ferrous citrate preparation>

126243

CONTRAINDICATIONS (FERROCYTE is contraindicated in the following patients.)
Patients who are not iron-deficient
[Since iron overload may occur, caution should be taken to avoid accidental overdosing.]

DESCRIPTION

1. Composition
Each white, gastric-soluble, film-coated tablet contains 470.9 mg of sodium ferrous citrate (50 mg as elemental iron).
It also contains carmellose, microcrystalline cellulose, titanium oxide, calcium stearate, low substituted hydroxypropylcellulose, hydroxypropylcellulose, hypromellose and macrogol 6000 as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
Ferrocyte Tablets 50 mg	Film-coated tablets	S 301			White
	S 301	Diameter (mm) 10.3	Weight (mg) 550	Thickness (mm) 5.0	

INDICATIONS

Iron-deficiency anemia

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 100-200 mg as elemental iron (2-4 tablets) daily in one or two divided doses after meals.
The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration (FERROCYTE should be administered with care in the following patients.)
(1) Patients with gastrointestinal diseases such as peptic ulcer, chronic ulcerative colitis or focal enteritis
[FERROCYTE may aggravate such conditions.]
(2) Patients with paroxysmal nocturnal hemoglobinuria
[FERROCYTE may induce hemolysis and aggravate the condition.]
(3) Patients on therapy with iron-containing preparations (iron preparations, liver-specific contrast media for MRI, etc.)
[Iron overload may occur.]

2. Important Precautions
Hematological tests should be conducted during treatment with FERROCYTE as necessary to avoid accidental overdosing.

3. Drug Interactions
Precautions for coadministration (FERROCYTE should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Cefdinir	FERROCYTE reduce the absorption of cefdinir to about one tenth, so FERROCYTE should be administered at intervals of 3 hours or longer.	FERROCYTE forms high molecular iron chelates with the other drug, and absorption of the other drug is inhibited.
Quinolone-type antimicrobial drugs Ciprofloxacin hydrochloride Norfloxacin Tosufloxacin tosilate hydrate Sparfloxacin, etc.	FERROCYTE may inhibit the absorption of antimicrobial drugs.	
Tetracycline-type antibiotics	Absorption is mutually inhibited.	FERROCYTE forms high molecular iron chelates with the other drug, and absorption is mutually inhibited.
Thyroid hormone preparations Levothyroxine sodium hydrate Liothyronine sodium, etc.	FERROCYTE may inhibit the absorption of thyroxine.	High molecular iron chelates are formed and may inhibit the absorption of thyroxine.
Antacids	Absorption of iron may be inhibited.	An in vitro study has reported that FERROCYTE and antacid form barely soluble iron polymers due to increasing gastric pH.
Foods containing tannic acid	Absorption of iron may be inhibited.	An *in vitro* study has reported that FERROCYTE and tannic acid form high molecular iron chelates.

4. Adverse Reactions
Adverse reactions were reported in 487 of 5,939 patients (8.20%). (At the end of the reexamination period)

	≥ 5%	5% > ≥ 0.1%	< 0.1%	Incidence unknown
Gastrointestinal	Nausea/vomiting	Upper abdominal discomfort, gastric or abdominal pain, diarrhea, anorexia, constipation and heartburn	Feeling of enlarged abdomen	
Hypersensitivity note)		Rash	Itching	Photosensitivity
Hepatic		Elevation of AST(GOT) and ALT(GPT), etc.	Elevation of Al-P, etc.	
Psychoneurologic			Headache and dizziness	
Others			Malaise and edema	

Note) In the event of such symptoms, FERROCYTE should be discontinued.

5. Use in the Elderly
Since the physiological functions of elderly patients are impaired in general, caution, such as dose reduction, should be exercised in these patients.

6. Pediatric Use
Safety of FERROCYTE for use in children has not been established (inadequate clinical experience).

7. Effects on Laboratory Tests
Occult blood tests may yield false-positive results.

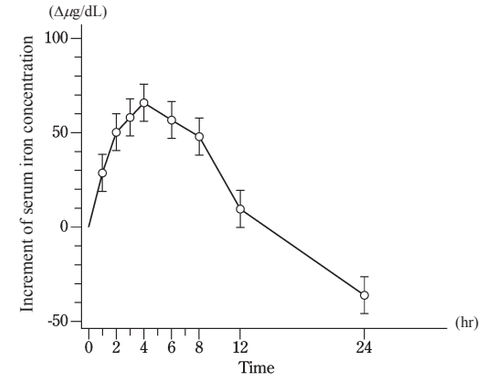
8. Overdosage
(1) Symptoms
Major symptoms of overdose are gastrointestinal symptoms including nausea, vomiting, abdominal pain, hemorrhagic diarrhea and hematemesis due to gastric mucosal irritation. Tachycardia, decreased blood pressure, cyanosis, elevated GOT, elevated GPT, etc., have also been reported. In the event of a serious disease, coma, shock, liver necrosis and hepatic failure may develop.
(2) Treatment
Therapeutic emesis and gastric lavage are effective in the early stages after administration of FERROCYTE. Other treatments include administration of cathartics, iron chelators (deferoxamine), etc. In cases where decreased blood pressure or circulatory collapse develops, symptomatic treatment using vasopressors, fluid therapy, etc., should be performed.

9. Precautions concerning Use
Caution when handing over drug (tablets)
For drugs that are dispensed in a press-through package (PTP), patients should be instructed to remove the drugs from the package prior to use. [Swallowing the PTP sheet by mistake has been reported to cause puncture in the esophageal mucosa due to sharp corners of the sheet, resulting in perforation and in serious complications such as mediastinitis.]

10. Other Precautions
(1) Stools may become dark due to the use of FERROCYTE.
(2) FERROCYTE may cause temporary discoloration (browning) of the teeth. In the event of this occurrence, the teeth should be brushed with sodium bicarbonate, etc.
(3) FERROCYTE coadministered with a large dose of allopurinol has been reported to increase iron reserve in the liver in an animal study.

PHARMACOKINETICS

1. Serum iron concentration
Two tablets of FERROCYTE (100 mg as elemental iron) were administered to 18 healthy adult male volunteers after a meal. The serum iron concentration increased at 1 hr, peaked at 3-4 hr, and returned to the pre-treatment baseline at 12 hr after administration.



Serum iron concentration after oral administration of FERROCYTE 2 Tablets after meal
Δ: Increment from pretreatment

5
7
6

Pharmacokinetic parameters after oral administration

ΔC_{max} (μg/dL)	t_{max} (hr)	ΔAUC (μg · hr/dL)
69.0±12.7	3.9±0.5	605±161

(Mean±S.D., n=18)

The serum iron concentration at 24 hr after administration was lower than the pre-administration level. This phenomenon is also seen with other iron preparations and is within daily range of physiological change. It has been suggested that this is due to a high transfer of iron from the serum into the iron reserve pool.

2. **Transfer to the fetus**
   Sodium ferrous citrate is transferred from the maternal body into the fetus as transferrin iron due to the physiological regulatory function of the placenta. Transferrin iron in the maternal body is converted into placental ferritin after transfer into placental tissues and then into fetal transferrin iron after crossing the placenta. Sodium ferrous citrate was more quickly absorbed and transferred to blood, placenta, fetuses and amniotic fluid than an analog compound (ferrous sulfate) in pregnant rats.
3. **Transfer to the milk**
   Sodium ferrous citrate is transferred to the blood as transferrin, and thereafter transferrin is transfer to the milk as lactoferrin. Sodium ferrous citrate was more quickly transferred to milk than an analog compound (ferrous sulfate) in nursing rats.

CLINICAL STUDIES

Clinical efficacy
Open labeled clinical trials have shown that FERROCYTE improved anemic symptoms (malaise, palpitations, shortness of breath and dizziness) and peripheral hematological findings (hemoglobin content, serum iron concentration, TIBC, serum ferritin concentration, RBC count and hematocrit value) in patients with iron-deficiency anemia.

	Moderately to remarkably improved
Improvement in anemic symptoms	98/110(89.1%)
Improvement in peripheral hematological findings	117/161(72.7%)

The rate of improvement of hemoglobin level and usefulness were significantly higher in the 200 mg/day of FERROCYTE group than in the 100 mg/day group. There was no difference in effectiveness between tablets and granules as regards increase in hemoglobin and alleviation of anemic symptoms.
FERROCYTE has also been shown to be useful in a double blind clinical trial.

(Reference)
In a pilot study on implementation methods for a clinical experience investigation, this was no difference in incidence rate of adverse reactions between pregnant and non-pregnant women in 545 patients.
A follow-up study on fetuses and neonates delivered from mothers who had administered FERROCYTE in drug use investigation showed that there were no problems.

Incidence rate of adverse reactions of pregnant women vs no pregnant women

	Pregnant women	Non-pregnant women
Patients	340	205
Cases of adverse reactions	26	15
Incidence rate (%)	7.65	7.32

A pilot study was conducted to compare the incidence rate of adverse reactions in elderly patients and non-elderly patients. In 1,254 patients, there was no significant difference in adverse reactions incidence rates between 60 years or over and under 60 for either men or women. However, the incidence rate for women was higher than for men.

Comparison of incidence rate of adverse reactions (AR) by age and sex

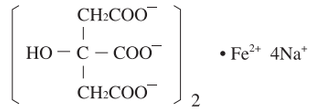
	men			women			total
	≥60	60>	total	≥60	60>	total	
Patients	139	130	269	206	779	985	1,254
Cases of AR	11	9	20	22	115	137	157
Events of AR	14	10	24	29	170	199	223
Incidence rate (%)	7.91	6.92	7.43	10.67	14.76	13.91	12.52

PHARMACOLOGY

1. **Mechanisms of action**
   Absorbed iron is bound to plasma transferrin and enters the general circulation. Iron bound to transferrin is taken into erythroblasts in bone marrow and used for synthesis of hemoglobin.
2. **Sodium ferrous citrate increases serum iron levels without being affected by gastric acid secretion.**
   Increases in serum iron levels achieved by sodium ferrous citrate were similar to those achieved by ferrous sulfate and ferrous fumarate in normal rabbits and rats, and anemic rabbits. When sodium ferrous citrate was administered to dogs after a meal, it increased serum iron levels.
   Sodium ferrous citrate increased serum iron levels in rats whose gastric acid secretion was inhibited, suggesting that gastric acid has relatively little effect on sodium ferrous citrate.
3. **Sodium ferrous citrate improves anemia through recovery of hemoglobin level and iron reserve.**
   The Hemoglobin level showed a marked recovery after administration of sodium ferrous citrate (30 mg/kg/day) for 18 consecutive days to exsanguinated anemic rats fed with iron deficient-food. The Iron content in the liver and spleen was significantly increased compared to the control, suggesting that the drug replenishes the iron reserve. Sodium ferrous citrate also improved lowered serum iron levels and the serum iron saturation index, and increased the total iron-binding capability.

PHYSICOCHEMISTRY

Nonproprietary name: Sodium Ferrous Citrate (JAN)
Chemical name: Tetrasodium biscitrato iron (II)
Molecular formula: $C_{12}H_{10}FeNa_4O_{14}$
Molecular weight: 526.01
Structural formula:



Description:
Sodium ferrous citrate occurs as a greenish white to green-yellowish white, crystalline powder. It is slightly soluble in water, and practically insoluble in ethanol (95). This product dissolves in dilute hydrochloric acid, dilute nitric acid and dilute sulfuric acid. This product gradually turns brown when exposed to light.

STORAGE FOR HANDLING

1. FERROCYTE should be stored below 30℃.
2. FERROCYTE should be protected from moisture after opening aluminum bag.
3. FERROCYTE should be used before the expiration date indicated on the package.

PACKAGING

Boxes of 100 in press-through packages

NOTE

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Manufactured by:
Alfresa Pharma Corporation Gunma Plant
3038-2, Serada-cho, Ota-shi, Gunma, Japan

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TOKYO, JAPAN

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