CONTRAINDICATIONS (FERROMIA 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
   Tablets 50 mg:
   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.

   Granules 8.3%:
   Each 1.2 g of greenish white to green-yellowish white granules contains 941.8 mg of sodium ferrous citrate (100 mg as elemental iron).
   It also contains aspartame (L-phenylalanine compound), hydroxypropylcellulose, D-mannitol and flavor as inactive ingredients.

2. Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dosage form and identification code</th>
<th>Appearance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERROMIA Tablets 50 mg</td>
<td>Film-coated tablets</td>
<td>S301 Diameter (mm) 10.3 Weight (mg) 550 Thickness (mm) 5.0</td>
<td>White</td>
</tr>
<tr>
<td>FERROMIA Granules 8.3%</td>
<td>Granules</td>
<td></td>
<td>Greenish white to green-yellowish white</td>
</tr>
</tbody>
</table>

INDICATIONS
Iron-deficiency anemia

DOSAGE AND ADMINISTRATION

FERROMIA Tablets 50 mg:
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.

FERROMIA Granules 8.3%:
The usual adult dosage for oral use is 100-200 mg as elemental iron (1.2-2.4 g) 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 (FERROMIA should be administered with care in the following patients.)
   (1) Patients with gastrointestinal diseases such as peptic ulcer, chronic ulcerative colitis or focal enteritis [FERROMIA may aggravate such conditions.]
   (2) Patients with paroxysmal nocturnal hemoglobinuria [FERROMIA 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 FERROMIA as necessary to avoid accidental overdosing.

3. Drug Interactions
   Precautions for coadministration (FERROMIA should be administered with care when coadministered with the following drugs.)
Cefdinir
FERROMIA may reduce the absorption of cefdinir to about one-tenth, so FERROMIA should be administered at intervals of 3 hours or longer.

FERROMIA forms high molecular iron chelates with the other drug, and absorption of the other drug is inhibited.

Quinolone-type antimicrobial drugs
Cyprofloxacin hydrochloride
Norfloxacin
Tosufloxacin tosylate hydrate Sparfloxacin, etc.
FERROMIA may inhibit the absorption of antimicrobial drugs.

FERROMIA forms high molecular iron chelates with the other drug, and absorption of the other drug is inhibited.

Tetracycline-type antibiotics
Absorption is mutually inhibited.
FERROMIA forms high molecular iron chelates with the other drug, and absorption is mutually inhibited.

Quinolone-type antimicrobial drugs
Cyprofloxacin hydrochloride
Norfloxacin
Tosufloxacin tosylate hydrate Sparfloxacin, etc.
FERROMIA may inhibit the absorption of antimicrobial drugs.

FERROMIA forms high molecular iron chelates with the other drug, and absorption is inhibited.

Tetracycline-type antibiotics
Absorption is mutually inhibited.
FERROMIA forms high molecular iron chelates with the other drug, and absorption is mutually inhibited.

Thyroid hormone preparations
Levothyroxine sodium hydrate
Liothyronine sodium, etc.
FERROMIA may inhibit the absorption of thyroxine.

FERROMIA forms high molecular iron chelates with the other drug, possibly leading to inhibition of the other drug.

Antacids
Absorption of iron may be inhibited.
An in vitro study has reported that FERROMIA 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 FERROMIA 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)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>≥5%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea/vomiting</td>
<td>Upper abdominal discomfort, gastric or abdominal pain, diarrhea, anorexia, constipation and heartburn</td>
<td>Feeling of enlarged abdomen</td>
</tr>
<tr>
<td>Hypersensitivity (non)</td>
<td>Rash</td>
<td>Itching</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevation of AST (GOT) and ALT (GPT), etc.</td>
<td>Elevation of AI-P, etc.</td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Headache and dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Malaise and edema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note) In the event of such symptoms, FERROMIA 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 FERROMIA for use in children has not been established (inaudited 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, 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 FERROMIA. 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 1, 2).

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 FERROMIA.
(2) FERROMIA may cause temporary discoloration (browning) of the teeth. In the event of this occurrence, the teeth should be brushed with sodium bicarbonate, etc.
(3) FERROMIA 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
In 18 healthy adult men who received 2 tablets of FERROMIA (100 mg as elemental iron) orally as a single dose after meals, the serum iron concentration increased from 1 hour after administration, peaked at 3-4 hours after administration, and returned to the level before administration at 12 hours after administration 3).
Serum iron concentration after oral administration
2 tablets of FERROMIA after meal
Δ: Increment from pretreatment

Increment of serum iron concentration
(Δμg/dL)

Pharmacokinetic parameters after oral administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>μg/dL</td>
<td>69.0 ± 12.7</td>
</tr>
<tr>
<td>tmax</td>
<td>hr</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>AUC</td>
<td>μg·hr/dL</td>
<td>605 ± 161</td>
</tr>
</tbody>
</table>

(ΔCmax, tmax, AUC: Mean ± S.D., n=18)

The serum iron concentration at 24 hours after administration was lower than the pre-administration level. This has also been seen with other iron preparations, and is within daily physiological variation and considered due to increased transfer of iron from the serum into the storage pool of iron.

2. Transfer to the fetus
Sodium ferrous citrate is transferred from the maternal body to the fetus as transferrin iron due to the physiological regulatory function of the placenta. That is, 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 hydrate) in pregnant rats.

3. Transfer to the milk
Sodium ferrous citrate is transferred to the blood as transferrin, and thereafter the transferrin is transferred to the milk as lactoferrin. Sodium ferrous citrate was more quickly transferred to milk than an analog compound (ferrous sulfate hydrate) in nursing rats.

CLINICAL STUDIES
Clinical efficacy
Open-labeled clinical trials have shown that FERROMIA 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.

| Improvement in anemic symptoms | 98/110 (89.1%) |
| Improvement in peripheral hematological findings | 117/161 (72.7%) |

The rates of improvement of hemoglobin level and usefulness were significantly higher in the FERROMIA 200 mg/day group than in the 100 mg/day group. There was no difference in effectiveness between tablets and granules with regard to increases in hemoglobin and alleviation of anemic symptoms.

FERROMIA 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 conducted in 545 women, no difference was observed in the incidence rate of adverse reactions between pregnant and non-pregnant women.

A follow-up study on fetuses and neonates delivered from mothers who had taken FERROMIA in a drug-use investigation showed that there were no problems.

Incidence rate of adverse reactions of pregnant and non-pregnant women

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Pregnant women</th>
<th>Non-pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with adverse reactions</td>
<td>130</td>
<td>205</td>
</tr>
<tr>
<td>Incidence rate (%)</td>
<td>6.92</td>
<td>7.32</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Number of patients with AR episodes</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of AR episodes</td>
<td>11</td>
<td>130</td>
</tr>
<tr>
<td>Incidence rate (%)</td>
<td>7.91</td>
<td>7.43</td>
</tr>
</tbody>
</table>

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 hydrate and ferrous fumarate in normal rabbits and rats, and anemic rabbits. When sodium ferrous citrate was administered to dogs after a meal, serum iron levels increased.
Sodium ferrous citrate increased serum iron levels in rats with suppressed gastric acid secretion, suggesting that gastric acid has relatively little effect on sodium ferrous citrate [13].

3. Sodium ferrous citrate improves anemia through recovery of hemoglobin level and iron reserve.

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. Iron content in the liver and spleen was significantly increased compared to the control group, 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 [14].

PHYSICOCHEMISTRY

Nonproprietary name:
Sodium Ferrous Citrate (JAN)

Chemical name: Tetrasodium bistrichromate iron (II)

Molecular formula: C₁₂H₁₀FeNa₄O₁₄

Molecular weight: 526.01

Structural formula:

\[
\text{CH}_2\text{COO}^- \quad \text{HO} - \text{C} - \text{COO}'^{-} \quad \frac{1}{2} \text{CH}_2\text{COO}'^- \quad \cdot \text{Fe}^{2+} \cdot 4\text{Na}^+
\]

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.

PRECAUTIONS FOR HANDLING

1. Tablets in a press-through package should be protected from moisture after opening the aluminum bag.
2. Tablets in a bottle should be protected from moisture after opening the cap.
3. Granules in a divided package should be protected from moisture after opening the aluminum bag.
4. Granules in a bottle should be protected from light and moisture after opening the cap. (Granules may be discolored by light, and may absorb moisture.)

PACKAGING

FERROMIA Tablets 50 mg:
Boxes of 100, 500 and 1,000 in press-through packages, and bottles of 500

FERROMIA Granules 8.3%:
Cans of 100 g and 500 g, and boxes of 720 g (1.2 g package×600)

REFERENCES


REQUESTS FOR LITERATURE AND PRODUCT INFORMATION SHOULD BE MADE TO:
Customer Drug Information Service
Free Dial: 0120-419-497
Eisai Co., Ltd.

Manufactured and marketed by:
Sannova Co., Ltd.
3038-2, Serada-cho, Ota-shi, Gunma, 370-0426

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