# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT
FERROZINC-G 40 mg/15 mg syrup

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml (1 spoon) syrup contains,

**Active substance(s):**
344 mg iron II gluconate equivalent to 40 mg iron$^{+2}$
105 mg zinc gluconate equivalent to 15 mg zinc

**Excipient(s):**

| | |
|---|---|
| Sorbitol (70%) (E420) | 1500 mg |
| Fructose | 750 mg |
| Sodium benzoate (E211) | 5 mg |
| Sodium cyclamate | 11.5 mg |
| Sodium chloride | 21.55 mg |
| Sodium hydroxide | 103 mg |
| Sodium acetate | 2.53 mg |
| Glycerine | 315 mg |

For the full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM
Syrup
Brown, aromatic odor (raspberry) oily syrup

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
It is used in cases of zinc deficiency with iron deficiency.

### 4.2 Posology and method of administration
**Posology/frequency of administration and duration of the treatment:**
Unless otherwise recommended by the doctor, it is used with a pipette by dividing into 2-3 doses per day in children. Each 0.5 ml pipette contains 4 mg iron and 1.5 mg zinc.

| **Age** | **Daily dose (ml)** | **Daily dose (mg)** |
|---|---|---|
| 6 months – 1 year | 1.5 ml with pipette | 12 mg iron, 4.5 mg zinc |
| 1 – 3 years | 2.0 ml with pipette | 16 mg iron , 6 mg zinc |
| 4 – 8 years | 4 ml with pipette | 32 mg iron , 12 mg zinc |
| 9 – 13 years | 6.0 ml with pipette | 48 mg iron , 18 mg zinc |
| 14 – 18 years | 10 ml (2 spoons) | 80 mg iron , 30 mg zinc |
| 18 years and older | 13 ml with pipette | 104 mg iron , 39 mg zinc |

Therapeutic doses of the drug are continued until hemoglobin levels reach normal levels. Then the treatment is continued for at least two months in the half dose to fill the iron stores. Because the stores are slow to fill, the total duration of treatment is approximately six months when administered orally.

**Method of administration:**
It is used orally.

**Additional information for on special populations:**
**Renal/Hepatic failure:**
It should not be used in patients with severe renal or hepatic failure.

**Pediatric population:**
There is no additional information on the use in the pediatric population.

**Geriatric population:**
There is no additional information on the use in the geriatric population.

**4.3. Contraindications**
This medicinal product is contraindicated in patients who are allergic to the active ingredients and other excipients of the syrup.

It should not be used in patients with iron overload, defective iron utilization (e.g. hemochromatosis, hemosiderosis, hemoglobinuria, lead anemia, sidero-achrestic anemia, thalassemia, and other hemoglobinopathies), anemia unrelated with iron deficiency (e.g. it may lead to iron overload in patients megaloblastic anemia due to vitamin B12 deficiency, hemolytic anemia, or thalassemia), or in patients receiving regular blood transfusions or parenteral iron treatment.

In patients with HIV infection, daily treatment should not be administered unless it is clinically established that the anemia is due to iron deficiency.

It is contraindicated in patients with alcoholism and hepatitis.

Iron preparations are contraindicated in patients with inflammatory bowel disease, intestinal strictures, diverticular disease, active peptic ulceration, regional enteritis, or ulcerative colitis.

Concomitant use with dimercaprol is contraindicated.

Use of zinc-containing products in copper deficiency is contraindicated.

**4.4. Special warnings and precautions for use**
Appropriate clinical and laboratory assessment should be performed prior to initiation of treatment, since this medicinal product will provide no benefits in anemia unrelated with iron deficiency, and may lead to iron deposition in the body. Iron preparations leads to darkening of the stool color. Patients should be warned about possible color change in stools before treatment is initiated.

Since iron preparations may cause blackening of the stools, they may lead to false results in fecal occult blood test.

This medicinal product may lead to darkening of the teeth. Therefore, the oral cavity should be rinsed with adequate amount of water after ingestion of the syrup.

It may lead to toxic iron deposition in children when used in excessive doses for prolonged periods of time without medical supervision.

Absorption may be impaired in patients who had gastrectomy.

In male patients, the cause of iron deficiency should be more carefully assessed.

Treatment should be discontinued within 3 months after correction of iron deficiency.

Since anemia associated with combined deficiencies may lead to microcytic anemia, vitamin B12 or folic acid levels should be checked in subjects resistant to treatment with iron supplementation.

Patients with gastric ulcers should be treated under medical supervision.

Excessive doses may lead to irritating/corrosive effects that may be associated with the necrosis or perforation of the gastrointestinal mucosa.

Care should be exercised in the treatment of subjects with impaired iron absorption.

Elderly patients should be treated carefully due to the risk of severe adverse reactions.

It is important to investigate the potential underlying causes of anemia prior to treatment (e.g. gastric erosions, or colon cancer)

Zinc accumulation may occur in patients with renal failure.

Prolonged or excessive intake of zinc may lead to copper deficiency.

Patients with the rare hereditary disorder of fructose intolerance should not use this medicine, as it contains fructose and sorbitol (70%) (E420).

This medicinal product contains 66.34 mg of sodium in each 5 ml. This should be taken into consideration in patients on a controlled sodium diet.

In children under 6 years of age, inadvertent intake of iron containing products at a dose of 60 mg/kg (7.5 ml/kg with pipette) may cause fatal toxicity. Therefore, these medicines should be kept out of the reach of children.

**4.5. Interaction with other medicinal products and other forms of interaction**

Concomitant administration of iron and probably of other heavy metals with acetohydroxamic acid may lead to decreased absorption through chelation.

Concomitant intake of iron and dimercaprol should be avoided due to the formation of toxic compounds.

Concomitant use of antacids containing calcium salts, antacids such as magnesium trisilicate and carbonate and other mineral supplements, bicarbonate, carbonate, oxalate, or phosphate containing drugs may result in decreased iron absorption due to the formation of insoluble or poorly soluble

compounds, leading to unresponsiveness to therapy. Iron containing medications should not be used 1 hour before or 2 hours after within these products.

Oral gold compounds should not be administered concurrently with iron; if absolutely necessary, these should be administered at least several hours apart.

Concomitant intake with salicylates, phenylbutasone, and oxyphenyl butasone may lead to irritation of the intestinal mucosa.

Benzidine test may yield positive results during iron treatment.

Trientine and zinc decrease the absorption of each other.

This product should not be taken together with penicillin derivatives due to the presence of zinc salts. Penicillamine reduces zinc absorption.

Zinc cause reduced absorption due to chelation with tetracycline; thus these two preparations should not be administered concurrently.

Iron preparations should not be taken simultaneously with tea (contains tannic acid), eggs, coffee, milk and dairy products due to reduced absorption. Also, whole grain bread and products containing grains (containing phytic acid) may reduce iron absorption.

Iron absorption is reduced when ingested concomitantly with zinc and trientine.

When taken together with cholestyramine, iron absorption may be reduced.

Concurrent intake of iron-containing preparations and penicillamine may reduce iron absorption and decrease the activity of penicillamine. Penicillamine and iron should be administered at least 2 hours apart.

Concomitant intake of iron and tetracycline may reduce iron absorption, leading to decreased therapeutic activity of both medications. If treatment with both medications is required, iron should not be taken within 3 hours before or 2 hours after tetracycline ingestion.

Ascorbic acid or citric acid may increase iron absorption.

Concomitant intake of iron with vitamin E may have an effect on the hematologic response in patients with iron deficiency anemia. High dose iron may elevate the daily vitamin E requirements.

Iron salts may decrease the absorption of aluminum and zinc salts; also concurrent intake of iron and zinc salts may decrease iron absorption.

Oral iron antagonizes the hypotensive effect of methyldopa.

Oral iron decreases the absorption of bisphosphonates (should be taken at least two hours apart), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin), entecapone, and mycophenolate.

Proton pump inhibitors may decrease the absorption of iron.

When medicines containing levothyroxine are taken simultaneously with FERROZİNC-G, the absorption is impaired. Therefore, the two medicines should be taken at least 2 hours apart. .

Iron may decrease the absorption of eltromobag (a 4 hour interval should be allowed between eltromopag and iron intake), nalidixic acid, levodopa, and carbidopa.

Oral chloramphenicol delays the plasma iron clearance and entry of iron into erythrocytes, and affects erythropoiesis.

Neomycin may affect iron absorption.

Zinc may decrease copper absorption.

Zinc decreases the absorption of quinolone antibiotics.

Calcium salts decrease the absorption of zinc.

High-fiber foods and dairy products may decrease zinc absorption.

Caution is advised in patients with intestinal tumors.

After normalization of hemoglobin levels, oral iron treatment should be continued until repletion of iron stores as monitored by serum ferritin levels.

Oral contraceptives may reduce plasma zinc levels.

Daily zinc doses exceeding 30 mg may reduce the absorption of sparfloxacin. Therefore, FERROZİNC-G and sparfloxacin should be taken at least 3 hours apart.

**Additional information for special populations:**
No interaction studies for special populations have been conducted.

**Pediatric population:**
No interaction studies in the pediatric population have been conducted.

**4.6 Pregnancy and lactation**
**General advise**
Pregnancy category: C

**Women of childbearing potential / Birth control (Contraception)**
The estimated total iron requirement during pregnancy is 680 mg. In women with inadequate iron stores prior to pregnancy, iron supplementation is required.

Oral contraceptives may reduce plasma zinc levels.

Pregnant and lactating women can use this medicinal product under medical supervision. The physician may prescribe this medicinal product to pregnant women after the assessment of risks and benefits.

**Pregnancy**

Oral administration of recommended daily intake of zinc was not associated with any adverse effects. Controlled studies in pregnant women showed no risk for the mother and fetus during the first trimester of the pregnancy. No evidence of risk was found during the first trimester.

No evidence of adverse effects has been observed for normal doses of iron gluconate in pregnant and lactating women.

However, as with all medicines, caution is advised during FERROZİNC-G treatment during pregnancy and lactation.

Animal studies are inadequate with regard to effects on pregnancy and/or embryonal/fetal development and/or birth and/or post-natal development. The potential risks for humans is unknown.

FERROZİNC-G should not be used during pregnancy unless necessary.

**Breast-feeding**
This product should be taken as prescribed by a doctor during pregnancy and lactation.

Iron is excreted into breast milk in negligible amounts (approx. 0.5 mg/day)

Zinc is excreted into breast milk.

**Reproduction ability / Fertility**
This medicinal product is not associated with any adverse effects on women of childbearing potential and contraception.

**4.7. Effects on ability to drive and use machines**
There is no negative effect on ability to drive and use of machines.

**4.8. Undesirable effects**
The specified undesirable effects are classified according to the following rule:
Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10.000); unknown (Frequency cannot be estimated from the available data).

**Blood and lymphatic system disorders:**
Uncommon: Neutropenia, leucopenia-anemia

**Immune system disorders:**
Rare: Allergic reactions

**Nervous system disorders:**
Uncommon: Dizziness, headache, nervousness, numbness

**Vascular disorders:**
Very rare: Hypotension, arrhythmia, electrocardiographic changes in potassium deficiency

**Gastrointestinal disorders:**
Rare: Fresh blood in the stool

Common: Diarrhea, nausea, epigastric pain, gastrointestinal irritation, epigastric fullness, dyspepsia, constipation, vomiting, darkening of stool color, gastritis

**Kidney and urinary tract disorders:**
Uncommon: darkening of urine color

These symptoms caused by irritation can be prevented by dose reduction or by taking the drug after meals. Please note that foods will prevent iron absorption

Oral liquid preparations containing iron salts may cause the discoloration of teeth. To prevent this, the mouth should be rinsed with water after use.

Excessive intake or incorrect treatment can lead to hemosiderosis.

Zinc can affect copper absorption and cause reduced copper levels and copper deficiency. The risk of copper deficiency is greater with long-term treatment and / or high zinc doses.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 800 314 00 08; fax: 0 312 218 35 99).

**4.9. Overdose and treatment**
Iron overdose:
High doses of iron (II) gluconate are toxic, although it rarely causes fatality in adults. In children between 1 and 2 years of age, iron dose between 1 and 2 grams may be fatal.

*Symptoms*
During the first phase of acute iron overload up to 6 hours following oral intake, the most common symptoms include gastrointestinal toxicity, excessive nausea, vomiting, abdominal pain, and diarrhea. Also hematemesis and rectal bleeding may occur. Other possible symptoms include metabolic changes including hypotension, tachycardia, acidosis, and hyperglycemia and central nervous system depression ranging from lethargy to coma. Patients with mild to moderate toxicity usually do not proceed to this stage.

The second phase occurs between 6 and 24 hours after oral intake and is characterized by temporary remission or clinical stabilization.

Shock, metabolic acidosis, convulsions, coma, hepatic necrosis and jaundice, hypoglycemia, coagulation disorders, oliguria or renal failure and pulmonary edema, and gastrointestinal toxicity may re-occur in third stage between 12 and 48 hours following oral intake. Also, severe lethargy and myocardial dysfunction may be observed.

The fourth phase may be observed several weeks after oral intake, and is characterized by gastrointestinal obstruction, and probably by late hepatic injury.

Prolonged and excessive iron doses may cause hemosiderosis. Hepatic cirrhosis and pancreatic fibrosis may develop due to iron accumulation.

*Treatment*
The following steps are recommended to reduce or prevent additional absorption. Gastric lavage should only be considered within 1 hour of ingestion of life-threatening doses, provided that adequate airway support is maintained.

Children:

1. Gastric lavage is more appropriate than emesis, except for cases with severe poisoning and unless emesis is absolutely necessary. If a decision to induce emesis is made, an emetic agent such as ipecac syrup is administered.

2. Gastric lavage with desferroxamine solution (2 g/l) is performed to remove the gastric content. This should then be followed by the instillation of desferrioxamine 5g in 50-100 ml water, to be retained in the stomach. It can be harmful because it causes diarrhea in children and should not be undertaken in young children. Keep the patient under constant surveillance to detect possible aspiration of vomitus - maintain suction apparatus and standby emergency oxygen in case of need.

3. Severe poisoning:
   In the presence of shock and/or coma with high serum iron levels (serum iron >90µmol/l) immediate supportive measures plus i.v. infusion of desferrioxamine should be instituted. Desferrioxamine 15mg/kg body weight should be administered every hour by slow i.v. infusion to a maximum 80mg/kg/day.

   Warning:
   Hypotension may occur if the infusion rate is too rapid

4. Less severe poisoning:
   i.m. desferrioxamine 1g 4-6 hourly is recommended.

5. Serum iron levels should be monitored.

Adults:

1. Gastric lavage is more appropriate than emesis, except for cases with severe poisoning and unless emesis is absolutely necessary. If a decision to induce vomiting is made, an emetic is administered.

2. Gastric lavage may be necessary to remove drug already released into the stomach. This should be undertaken using desferrioxamine solution (2g/l). Desferrioxamine 5g in 50-100ml water should be introduced into the stomach following gastric emptying. Keep the patient under constant surveillance to detect possible aspiration of vomitus; maintain suction apparatus and standby emergency oxygen in case of need.

3. A drink of mannitol or sorbitol should be given to induce small bowel emptying.

4. Severe poisoning:
   In the presence of shock and/or coma with high serum iron levels (>142µmol/l) immediate supportive measures plus i.v. infusion of desferrioxamine should be instituted. The recommended dose of desferrioxamine is 5mg/kg/h by slow i.v. infusion up to a maximum of 80mg/kg/day.

   Warning:

Hypotension may occur if the infusion rate is too rapid.

5. Less severe poisoning:
   i.m. desferrioxamine 50mg/kg up to a maximum dose of 4g should be given.

6. Serum iron levels should be monitored.

Zinc overdose
Zinc salts exert corrosive effects when ingested in excessive doses. The signs of overdose include corrosion, and inflammation of the oral and gastric mucosa; perforation may occur following gastric ulceration. Induction of vomiting should be avoided, unless absolutely necessary. Gastric lavage should only be considered within the 1st hour after ingestion of life-threatening doses of iron, if adequate airway support is maintained. Liquids such as milk can be ingested for protection. Also, chelation agents such as calcium edetate may be beneficial.

No cases of chronic zinc toxicity have been described in humans. Long term or high dose administration of zinc may lead to copper deficiency and anemia. In such cases, 4 mg/day of copper sulfate may be required for correcting the copper deficiency, and slow blood transfusions may be required for anemia.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Various combinations with iron
**ATC Code:** B03AE10

Iron is an essential constituent of the body. It has important functions such as hemoglobin formation in blood, carrying oxygen into the tissues, maintenance of oxidative processes. Ferrous fumarate, a salt including valence 2 ferrous in large amounts, is used in cases when the need for iron is increased e.g. during pregnancy and for the treatment of iron deficiency anemia. Ferrous (+2 valence) salts are absorbed from the gastrointestinal tract threefold more than iron salts in the ferric (+3 valence) form. Zinc is a metal found in the structure of various enzymes such as dehydrogenase, aldolase peptidase phosphotase, isomerase, phospholipase, which have important roles in carbohydrate, protein and lipid metabolism Also, it is present in pyridine nucleotide dependent enzymes in large amounts and serves as a cofactor in many enzyme systems. As a result of zinc deficiency of organism protein and carbohydrate metabolism is impaired, learning capacity diminishes and retarded growth occurs. Zinc has multiple functions such as DNA and RNA, protein synthesis, insulin activation, wound healing, cell division, taste, sperm formation, and immunity.

Zinc is required for the proper functioning of more than 2000 metalloenzymes including carbonic anhydrase, carboxypeptidase A, alcohol dehydrogenase, alkaline phosphatase, and RNA polymerase. Zinc is mainly used for DNA, RNA, and protein stabilization. Zinc is required for a number of physiological functions such as the production of nucleic acids, proteins, and cell membranes; cell growth and division; sexual maturation and reproduction; wound healing; immunity; dark adaptation and night vision; and intact taste and smell. The biochemical functions of zinc become more evident in cases with zinc deficiency. Tissues with high growth rate (connective tissues in the wound granulation, sperm, embryo, fetal cells) are more markedly affected by the deficiency.

Acute toxicity risk associated with oral intake of zinc compounds is low. Single oral doses of 1 to 2 g of zinc sulfate (134-168 ml: 1.5-2.5 bottles) may lead to toxic effects, and single oral doses of 3 to 5 g of zinc sulfate (403-373 ml: 4-7 bottles) may lead to death in adults.
Even with oral intake of higher therapeutic doses (as high as 660 mg/day) has not been reported to cause chronic toxicity. Plasma copper levels should be monitored for potential decline.

**5.2. Pharmacokinetic properties**
**General characteristics**
Absorption and bioavailability
Iron gluconate exhibits linear pharmacokinetics at a dose range of 1.5 to 3 mg/kg. When administered orally, absorption depends on the condition of the patient. The absorption is within 3 to 10% in normal individuals while increasing 20 to 30% in those with iron deficiency. The absorption is more favorable on an empty stomach.

Zinc exhibits a non-linear saturation curve. An examination of the metabolism of zinc showed partial absorption from the gastrointestinal tract following oral intake. Bran bread, milk, cheese, and coffee may reduce the absorption.

Distribution
Iron is 90% bound to plasma proteins and hemoglobin.

2 to 8% of ionic zinc in blood is bound to low molecular weight serum proteins. Its usual plasma concentration is between 0.7 and 1.5 μg/ml. Plasma concentration of a patient orally receiving 50 mg of elemental zinc is reached approximately to 2.5 μg/ml within 2 to 3 hours.

Highest concentrations of zinc occur in hair, eyes, male genital organs, and bones, while tissue levels are lower in the liver, kidneys, and muscles. Of the circulatory zinc, 80% is within erythrocytes. Plasma zinc levels range between 70 and 110 μg/dL, and 50% is weakly bound to albumin. Approximately 7% is bound to amino-acids, while the remaining exhibit strong binding to alpha 2-macroglobulins and other proteins.

Biotransformation
Iron is kept in plasma with a dynamic balance. While new transferrin-iron complex is formed with the intestinal iron, major fraction of iron (~80%) which is carried as a combination with transferrin in plasma, is transferred to the precursor cells in bone marrow and hepatic reticuloendothelial cells. Iron-transferrin complex enters into cells via receptor-mediated endocytosis, is taken into a nonlysosomal acidic vesicle and disassociated from the iron-complex, the remaining apotransferrin receptor complex returns to the membrane and is used here. Iron joins to protoporphyrin and is converted to hem after being transferred to erythroid cells or mitochondrias or stored as being combined with ferritin. Number of receptors increases in case of iron deficiency. The plasma half-life of iron is 1.5 hours.

Elimination
No physiological elimination systems exist for iron. However small amounts may be removed through the skin, hairs, nails, feces, breast milk, menstruation blood, and urine. The plasma half-life is 1.5 hours.

Excretion of zinc occurs via the feces. Small amount of it is excreted via urine. Of the 13.2 mg zinc, which is the daily dietary intake of a normal adult, 5.6 mg is excreted via the feces and 0.1-0.9 mg through the urine. The kidneys normally have no impact on the regulation of serum zinc and shows highly limited elimination capacity. Even though the amount of orally taken zinc is

increased, excretion via the urine does not change, however, when zinc is administered intravenously apparent increase in urinary excretion occurs. Biliary excretion of zinc is very limited when compared to the urinary excretion. Zinc loss via the sweat may be observed. It is reported that 2-3 mg of zinc is lost via the sweat in hot climate. The plasma half-life is 3 hours.

**5.3. Preclinical safety data**
Not available.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**
Sorbitol (70%) (E420)
Sodium benzoate (E211)
Fructose
Neohesperidin DC
Sodium cyclamate
Sodium chloride
Sodium hydroxide
Sodium acetate
Citric acid
Glycerine
Raspberry aroma
Deionized water

**6.2. Incompatibilities**
There is no evidence that FERROZINC-G is incompatible with any drug or substance.

**6.3. Shelf life**
24 months

**6.4. Special precautions for storage**
Store at room temperature below 25ºC.

**6.5. Nature and contents of container**
FERROZINC-G is marketed in amber colored glass bottle (Type III) containing 100 ml of syrup closed with pilfer-proof high density polyethylene (HDPE) cap and low density polyethylene (LDPE) seal.

Each carton box contains one bottle and one pipette of 5ml.

**6.6. Special precautions for disposal and other handling**
Any unused product or waste material should be disposed of in accordance with “Directive on Control of Medical Waste” and “Directive on the Control of Packaging and Packaging Waste”.

## 7. MARKETING AUTHORIZATION HOLDER

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**8. MARKETING AUTHORIZATION NUMBER(S)**
226/8

**9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION**
Date of first authorization: 23.07.2010
Date of latest renewal: 16.09.2015

**10. DATE OF REVISION OF THE TEXT**
26.10.2018