SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FERROZINC Syrup, 100 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml (1 measuring cup) contains,

Active substances:

Equivalent to 39.77 mg iron	121 mg ferrous fumarate
Equivalent to 15 mg zinc	66 mg zinc sulphate heptahydrate
Folic acid	200 mcg
Vitamin C	50 mg

Excipients:

Sorbitol (70%) (420)	1500 mg
Methyl paraben sodium (E219)	5 mg
Sodium saccharin	1 mg
Fructose	750 mg
Sodium hydroxide	125 mg
Sodium chloride	21.55 mg
Sodium acetate	2.53 mg
Sodium cyclamate	5 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup
Brown, aromatic odor syrup

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

FERROZINC is used in cases of zinc deficiency with iron deficiency.

4.2. Posology and method of administration
Posology / Frequency and duration of administration:
If not recommended otherwise by the doctor, it may be used at the following doses:

Age range	Recommended zinc amount (mg/day)	Maximum tolerated amount of zinc (mg/day)	Scale (pipette)
7-12 month	3	5	1-1,5 mL
1-3 years	3	7	1-2 mL
4-8 years	5	12	1,5-4 mL
9-13 years	8	23	2,5-7,5 mL
14-18 years	11	34	3,5-11 mL
19 years and above	11	40	3,5-13 mL

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

Before the first use, FERROZINC should be prepared by mixing the powder mixture in the reservoir cap and the syrup in the bottle containing the mineral mixture. For instructions on preparing the product, see Section 6.6.

Additional information on special populations
Renal/ hepatic failure
It should not be used in patients with severe renal and hepatic failure.
The efficacy and safety of zinc in patients with suffered from renal and hepatic failure have not been studied.

Pediatric population:
Zinc should be administered to pediatric patients as described in the posology section. It should not be used in infants aged 0-6 months, since dose adjustment cannot be made unless recommended otherwise by the doctor.

Geriatric population:
No additional information is available on the use of FERROZINC in elderly patients. The efficacy and safety of zinc in geriatric patients have not been studied.

4.3. Contraindications
FERROZINC is contraindicated in the following situations:

- Hypersensitivity to active substances and other ingredients in the syrup
- Hemosiderosis
- Hemochromatosis
- Lead anemia
- Sidero acrestic anemia
- Thalassemia
- Megoblastic anemia due to lack of B12
- Hemolytic anemia
- Hemoglobinopathies
- Inflammatory bowel disease
- Intestinal strictures
- Diverticulum
- Active peptic ulcer
- Recurrent blood transfusions
- Enteritis (regional)
- Ulcerative colitis
- Anemia not dependent on iron deficiency
- Simultaneous use with parenteral iron
- Simultaneous use with dimercaprol
- Copper deficiency
- Alcoholism and hepatitis

- In HIV-infected patients, no daily treatment should be performed unless anemia due to iron deficiency is clinically confirmed.

4.4. Special warnings and precautions for use

Because iron preparations cause the darkening of stool colour, it can lead to incorrect results in fecal occult blood tests

Darkening may occur in the teeth. Therefore, the mouth should be rinsed with plenty of water after use.

Prolonged and excessive use without medical supervision can cause toxic accumulation in children.

Patients who have undergone gastrectomy may have impaired absorption.

The cause of iron deficiency in male patients should be investigated more carefully.

The duration of treatment should not exceed 3 months after treatment of iron deficiency.

Since anemia due to combined deficiencies may be of microcytic type, vitamin B12 or folic acid deficiency should be considered in patients with microcytic anemia who are resistant to treatment with iron.

It should be given to patients with gastric ulcer under medical supervision.

It can lead to zinc accumulation in renal failure.

Long term or high dose zinc intake may cause copper deficiency.

Accidental ingestion of iron-containing products in children can lead to fatal poisoning. Keep this medicine out of reach of children.

It is not appropriate to use zinc in adult with diarrhea of unknown cause.

Products containing 30 mg of zinc are not suitable for use in the treatment of pediatric patients with diarrhea due to the high amount of zinc given at one time.

Patients with rare hereditary fructose intolerance should not use this drug because it contains fructose and sorbitol (E420).

FERROZINC contains methyl paraben sodium (E219). Therefore, allergic reactions (possibly delayed) may occur.

This medicinal product contains 82.3 mg sodium per each 5 ml. This should be considered for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Iron reduces fluoroquinolone, levodopa, carbidopa, entacapone, bisphosphonate, mycophenolate and levothyroxine absorption

Calcium, magnesium and other mineral supplements, bicarbonates, carbonates, zinc and trientine reduce iron absorption.

Ascorbic acid or citric acid increases iron absorption.

Co-administration with vitamin E may affect the hematological response in patients with iron deficiency anemia. At higher doses, iron may increase the need for daily vitamin E.
Proton pump inhibitors can reduce oral iron absorption.

Iron can reduce eltrombopag (Eltrombopag and iron should be taken with 4 hour intervals) and nalidixic acid absorption.

Neomycin can affect iron absorption.

Iron reduces the hypotensive effect of methyldopan.

Chloramphenicol delays iron clearance from plasma and entry into red blood cells, affects erythropoiesis.

Zinc reduces copper absorption.

Zinc reduces absorption of quinolone group antibiotics.

Calcium salts reduce zinc absorption.

Treatment may be unresponsive when taken with antacids such as magnesium trisilicate and carbonate.

Milk and eggs decrease iron absorbance.

Iron and tetracycline reduce each other's absorption.

It should not be given with tetracycline, cholestyramine, antacids, penicillamine and oral gold compounds. If absolutely necessary to be taken, it should be given with few hours intervals.

Combinations with salicylates, phenylbutazone and oxyphenbutazone may cause irritation of the intestinal mucosa.

Benzidine test may give positive results during treatment with iron.

Cytostatics, sulphonamides, antiepileptics and barbiturates may reduce the absorption of folic acid.

Trientine and zinc reduce each other's absorption.

Due to its zinc salt, it should not be taken with penicillin derivatives. Penicillamine reduces zinc absorption.

Zinc sulphate chelates with tetracyclines and reduces its absorption; therefore concomitant use should be avoided.

It should not be taken with tea, coffee and milk.

It should be used with caution in those with bowel tumors.

After hemoglobin levels return to normal oral iron therapy must be continued until body iron stores are replenished while monitoring serum ferritine values.

Oral contraceptives may reduce plasma zinc level.

Absorption of sparfloxacin may reduce when zinc is used above 30 mg per day. Therefore, FERROZINC should be taken at least 3 hours after sparfloxacin.

When the drugs containing levothyroxine are taken with FERROZINC, the two drugs should be taken at least 2 hours apart as the absorption of FERROZINC is impaired.

4.6. Pregnancy and lactation
General recommendation:
Pregnancy category: C

- Despite this pregnancy category, the doctor should be made final decision by making a detailed benefit-risk assessment according to the gestational week, the existing/detected disease of the pregnant woman and other characteristics, on whether a pregnant woman should take the drug or not
- Although the risk categories help the healthcare staff about the potential risk of the drug in pregnancy, the evaluation of the physician is essential.

Women with childbearing capacity / Birth control (Contraception)
Total iron requirement of 680 mg during pregnancy is calculated. Iron supplementation is necessary in women who have insufficient iron stores before pregnancy.
Oral contraceptives may reduce plasma zinc levels.

Pregnancy
There is inadequate data on the use of FERROZINC in pregnant women.

Zinc given as much as the daily requirement from the oral route in pregnancies did not cause any problems. Controlled studies on pregnant women do not reveal a risk to mother and fetus during the first trimester of pregnancy. There were no signs of risks in the first trimester.

However, drug use in the first trimester of pregnancy should be done after careful consideration of potential risk / benefit, and drug use should be avoided unless it is clearly necessary. Iron treatment can be applied under physician advice in the rest of your pregnancy.

Animal studies are unsatisfactory in terms of effects on pregnancy / and-or/ embryonic / fetal development / and-or / natal / and-or/ postnatal development. Potential risk for humans is not known.

FERROZINC should not be used during pregnancy unless it is necessary.

Lactation
It should be used as prescribed by doctor and under medical supervision during pregnancy and lactation.

Zinc is excreted in breast milk.

There were no adverse effects related to iron fumarate in children who received breast milk and in their mothers. Iron fumarate can be used during lactation if clinically necessary.

Reproduction ability / Fertility
There are no negative effects on women with childbearing capacity or contraception.

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

4.8 Undesirable effects
The specified side effects are classified according to the following frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10.000 to <1/1.000); very rare (<1/10.000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: Neutropenia, leukopenia-anemia

Immune system disorders
Rare: Allergic reactions

Nervous system disorders
Uncommon: Headache, dizziness, nervousness, drowsiness

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

Gastrointestinal disorders
Rare: fresh blood in stools
Common: diarrhea, nausea, epigastric pain, gastrointestinal irritation, epigastric fullness, dyspepsia, constipation, vomiting, darkening of stool color, gastritis

Renal and urinary disorders
Uncommon: darkening of urine colour

These symptoms caused by irritation can be prevented by reducing the dose or taking the medicine after meals. It should not be forgotten that food will prevent iron absorption.

Oral liquid preparations containing iron salts can lead to darkening of teeth. To avoid this, the mouth should rinse with water after use.

Overdose or wrong treatment can lead to hemosiderosis.

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

4.9 Overdose
Overdose with iron

Symptoms
Gastrointestinal toxicity, excessive nausea, vomiting, abdominal pain and diarrhea usually occur in the first stage of acute iron overdose up to 6 hours after oral intake. Hematemesis and rectal bleeding may also occur. Metabolic changes including hypotension, tachycardia, acidosis and hyperglycemia, and central nervous system depression and other effects ranging from lethargy to coma can be seen. Patients with mild to moderate poisoning usually do not progress to this stage.

The second stage is seen after 6 to 24 hours of oral intake and is characterized by transient remission or clinical stabilization.

Shock, metabolic acidosis, convulsions, coma, hepatic necrosis and jaundice, hypoglycemia, coagulation disorders, oliguria or renal failure and gastrointestinal toxicity with pulmonary edema occur in the third stage after 12 to 48 hours of oral intake. In addition, severe lethargy and myocardial dysfunction may occur.

The fourth stage can be seen several weeks after oral intake and is characterized by gastrointestinal obstruction and possibly late hepatic injury.

Hemosiderosis is seen after long-term and overdose. Iron accumulation may lead to liver cirrhosis and pancreatic fibrosis.

Treatment
The following steps are recommended to reduce or prevent further absorption. Gastric lavage should be considered within 1 hour only after intake of the life-threatening amount if the respiratory tract is adequately protected.

Children:

1. It would be more appropriate to have gastric lavage instead of emesis of the patient except for severe poisoning and unless obliged. When it is decided to induce emesis, an emetic such as syrup of ipecacuanha is administered.

2. To remove the drug in stomach, gastric lavage with desferrioxamine solution (2 g / l) is performed. Then, Desferrioxamine 5g in 50-100ml water should be introduced into the stomach. Because it leads to diarrhea, it can be harmful to children and should not be given to 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 > 90 µmol/1) immediate supportive measure plus IV infusion of desferrioxamine should be instituted. Desferrioxamine 5mg/kg/hour should be administered by slow IV infusion to a maximum 80mg/kg/day.

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

4. Less severe poisoning:
   1 g desferrioxamine IM is recommended every 4 to 6 hours.

5. Serum iron levels should be monitored

Adults:

1. It would be more appropriate to have gastric lavage instead of emesis of the patient except for severe poisoning and unless obliged. When it is decided to induce emesis, an emetic is administered.

2. To remove the drug in stomach, gastric lavage with desferrioxamine solution (2 g / l) is performed. Then, 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 (>142umol/1) immediate supportive measures plus IV infusion of desferrioxamine should be instituted. The recommended dose of desferrioxamine is 5mg/kg/h by a slow IV infusion up to a maximum of 80 mg/kg/day.

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

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

6. Serum iron levels should be monitored.

Overdose with zinc

Zinc sulphate is corrosive in case of overdose. The overdose signs are corrosion, inflammation of the mucous membrane covering the mouth and the stomach, and perforation following penetration of the stomach ulceration. Unless obliged, it should be avoided without vomiting. Gastric lavage should be considered within 1 hour only after intake of the life-threatening amount if the respiratory tract is adequately protected. Preservatives such as milk should be given. Chelating agents such as sodium calcium edetate may be useful.

No chronic zinc poisoning has been detected in humans.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin, mineral combinations
ATC code: A11JB

FERROZINC is a medicine meeting the increasing requirements of organism in development period, pregnancy, confinement, time of recovery after illnesses completely and in a natural way. Following oral administration of FERROZINC, iron is rapidly absorbed and is used in hemoglobin and myoglobin synthesis or is transferred to iron stores. Consequently iron deficiency symptoms disappear with iron salts that are absorbed 3 times faster than in ferric form. Total body iron store is approximately 50 mg/kg in males and 35 mg/kg in females. Approximately 30% of iron is stored particularly in reticuloendothelial cells of liver, spleen and bone marrow in ferritin or hemosiderin.

Zinc plays an important role in folic acid metabolism and is a trace element found in the structure of various enzymes such as dehydrogenase, aldolase, peptidase, carboxypeptidase, phosphatase, isomerase, phospholipase which are essential in carbohydrate, protein and lipid metabolisms. Moreover it is abundant in enzymes bound to pyridine nucleotides and plays important role as cofactor in various enzymes. As a result of zinc deficiency in organism, protein and carbohydrate metabolism is impaired, learning capacity is inhibited and growing process slows down. In children with beta-thalassemia serum zinc levels are found to be low and these children presented same level of development as healthy children with the administered zinc therapy. Zinc has multifunctional roles in DNA and RNA, protein synthesis, insulin activation, wound healing, cell division, tasting, sperm production, immunity.

The acute toxicity of oral zinc compound is low. For adults, the use of the 1-2 g of zinc sulphate (134-168 ml: 1.5-2.5 bottles of syrup) at a time may lead to toxic symptoms and the use of the 3-5 g of zinc sulphate (403-373 ml: 4-7 bottles of syrup) at a time may lead to death.

It has been noted that symptoms of chronic toxicity which may occur with oral administration of the high therapeutic doses(even at doses of 660 mg/day) for a long time were not detected. It should be monitored whether the plasma copper levels are decreased.

Among the factors affecting erythropoiesis, folic acid plays an important role as well as iron. It has important functions in forming hemoglobin in blood, carrying oxygen to tissues, continuing oxidative process. Especially in pregnancy and breastfeeding, the need for folic acid in body increases. In formula of FERROZINC which is the appropriate combination of folic acid, zinc and Vitamin C together with iron which is well-assimilated in the organism, Vitamin C raises the absorption of iron to a maximum level, while also eliminating vitamin C deficiency.

Vitamin C plays an important role in the development of teeth and bone by helping to collagen and bone tissue forming. This increases body resistance. It also ensures optimum absorption of calcium and prevents leaking out of the capillaries of red blood cells.

5.2 Pharmacokinetic properties

General properties

Absorption and bioavailability:

Absorption of ferrous fumarate, when orally administered, varies depending on patient's condition. 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.

The saturation curve for zinc is non-linear. Given its metabolism, zinc is partially absorbed from the gastrointestinal tract when given via oral route. Food such as whole-wheat bread, milk, cheese and coffee decrease the absorption.

Absorption of folic acid is through duodenum and upper part of the jejunum. Total folate derivatives stored in tissues is about 70 mg and almost half of this is stored in liver cells. The concentration of folate derivatives in blood is approximately 300 ng/ml and more than 90% is in erythrocytes. Folate level in erythrocytes can be useful in monitoring folic acid deficiency.

Vitamin C plays a helpful role in the absorption of both iron and folic acid. Vitamin C is easily absorbed from gastrointestinal tract with a saturable transport.

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

Zinc; 2 to 8% of ionic zinc in blood is bound to low molecular weight serum proteins. 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.

The highest zinc concentration is seen in hair, eyes, male reproductive organs and bones. It is in the liver, kidney and muscles at lower levels. It is found in erythrocytes by 80%. The plasma zinc level is between 70 and 110 µg / dl, and approximately 50% is weakly bound to albumin. Approximately 7% is bound to amino-acids and the remainder is strongly bound to alpha 2-macroglobulins and other proteins.

Vitamin C is distributed over a wide area in the body, including intracellular. It is stored in the body. It binds to proteins at low levels. It is found in secretory glands, leukocyte, liver and eye lens at highest concentrations.

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.

Vitamin C is hepatically biotransformed. Vitamin C is partially converted to oxalic acid in the liver and forms part of the oxalate in the urine.

Elimination:
There is no physiological elimination system for iron. However, it is excreted in small amounts through the skin, hair, nail, feces, breast milk, menstruation 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.

Vitamin C is mainly eliminated from the kidneys. As with glucose, a threshold value is available in excretion with kidney. The threshold value is approximately equal to the plasma saturation concentration of vitamin C of 1.4 mg / dL. Above this concentration, the reabsorption maximum in the kidney proximal tubules is exceeded and the excess of vitamin C filtered through the glomerulus can not be absorbed and rapidly excreted in the urine. Therefore, there is no benefit in giving too much vitamin C.

Linearity/non-linearity:
Pharmacokinetics is linear. Plasma levels show an increase depending on the dose given.

5.3. Preclinical safety data
Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sorbitol (70%) (E420)
Methyl paraben sodium (E219)
Sodium saccharin
Citric acid monohydrate
Sodium hydroxide
Sodium chloride
Sodium acetate
Neohesperidin DC 98%
Fructose
Sodium cyclamate
Orange flavor
Lemon flavor
Tangerine flavor
Vanilla flavor
Purified water

6.2. Incompatibilities
There is no evidence regarding incompatibility of FERROZINC with any medicine or substance.

6.3. Shelf life
24 months

6.4 Special precautions for storage
Store in room temperature below 25°C.
The ready-to-use syrup is stable for 20 days when stored at room temperature below 25 °C.

6.5 Nature and contents of container
Primary packaging material is opaque white high-density polyethylene (HDPE) bottle closed with a reservoir cap system consisting of an opaque white polyethylene (PE) outer cap, a translucent polyethylene (PE) plug and a polypropylene (PP) plunger.

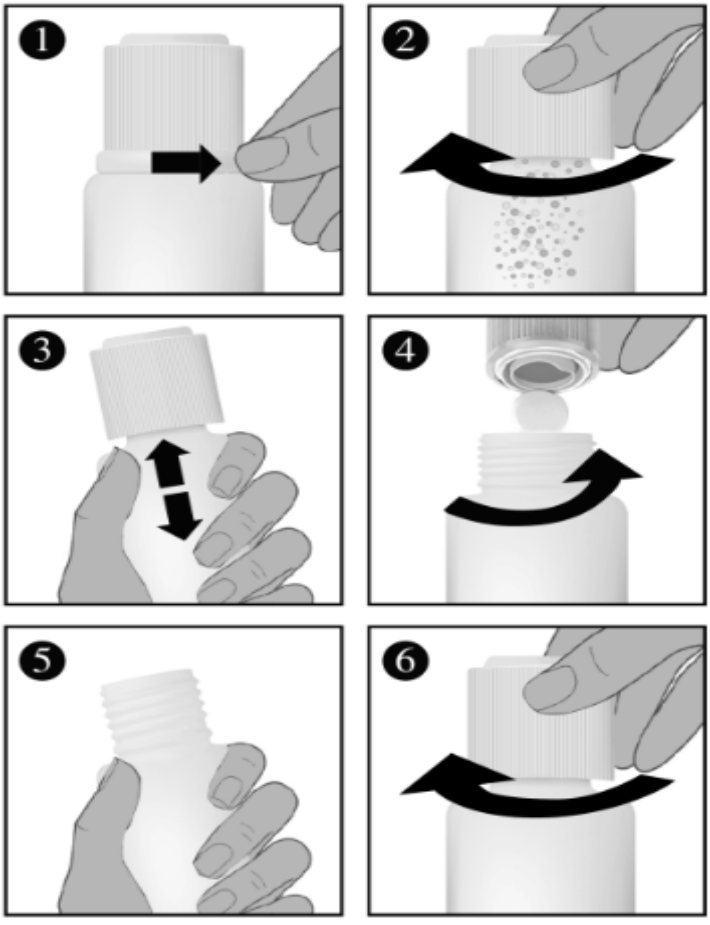
Primary packaging which is belong to the syrup containing mineral (Iron and Zinc) mixture:
Opaque white high-density polyethylene (HDPE) bottle closed with a reservoir cap system

Primary packaging which is belong to the reservoir cap containing vitamin (Folic acid and vitamin C) mixture:
Reservoir cap system consisting of an opaque white polyethylene (PE) outer cap, a translucent polyethylene (PE) plug and a polypropylene (PP) plunger.

Each box contains 100 ml x 1 bottle and 1 pipette with 5 ml.

6.6 Special precautions for disposal
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 Package and Packaging Waste".

Preparation of syrup before use:
Before use, the powder mixture in the reservoir cap is mixed with the syrup in the bottle containing the mineral mixture by following the steps below.



1. Open the safety ring by pulling the extension of the safety ring at the bottom of the cover
2. Turn the cap to the clockwise.
3. Shake the bottle well for 1-2 minutes.
4. Open the cap by turning counter-clockwise.
5. Use the appropriate dose of syrup by pipette.
6. Close the cap by turning clockwise.

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER(S)
210/19

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION
Date of first authorization: 19.12.2006
Date of latest renewal: 04.12.2018

10.DATE OF REVISION OF THE TEXT
18.05.2021