Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Amifer®
Iron- Folic acid- Cyanocobalamin

1.1. Strength

Elemental iron 30 mg/5ml – Folic acid 2.5 mg/5ml- Cyanocobalamin 0.02mg/5ml

1.2. **Pharmaceutical form** Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of syrup contains 30 mg of iron as Ferric ammonium citrate , 2.5 mg of Folic acid and 0.02 mg of cyanocobalamin (vitamin B12).

Excipients with known effect : Ethanol-Sorbitol-Ponceau 4R (E124)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution, Syrup
Brownish green to dark brown solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Prophylaxis and treatment of iron and folic acid deficiencies during pregnancy and the following weeks as well as during breastfeeding. Specific prophylaxis is also recommended during the second and third trimesters of pregnancy.
- Treatment of iron deficiency anaemia. It is essential to make an accurate diagnosis before starting treatment.

- Treatment preventing iron and folic acid deficiencies in case of low dietary iron and folic acid supplementation.
- Prevention of neural tube defects with folic acid is recommended before conception and during the first trimester of pregnancy

4.2. Posology and mode of administration

4.2.1. Posology

The posology and the period of treatment depends on the level of iron deficiency.

Posology for Iron supplement		
Age	Quantity of Iron mg/day	Quantity of Amifer ml/day
• Children 1 – 13 year • Adolescents 14 –18 year • Adults ≥ 19 year • Pregnancy and breast feeding	30 mg 60 mg 60 mg 60 mg	5 ml 10 ml 10 ml 10 ml
Posology for the treatment of severe anaemia		
Age	Quantity of Iron mg/day during 3 months	Quantity of Amifer ml/day
• Adolescents (14 –18 year) • Adults (≥ 19 year) • Pregnancy and breast feeding	120 mg 120 mg 120 mg	20 ml 20 ml 20 ml

4.2.2. Special populations

No special dosage recommendations

4.2.3. Pediatric population

For infants and children who solemnly need treatment with an iron supplement, sole-ingredient iron syrup (as iron-hydroxide-polymaltose complex), Amifer® Junior, is available.

4.2.4. Method of administration

Oral use by means of a dosing device.

Shake the bottle well before each use.

An interval of two to three hours should be applied between administration of Amifer syrup and a milky drink, coffee or tea.

Iron preparations must be taken at least 1 hour before or 2 hours after the administration of antacids and mineral supplements containing aluminium, calcium or magnesium, in order to avoid any reduction in iron resorption.

4.3. Contraindications

- Hypersensitivity to iron, to folic acid, to vitamin B12 or to any excipient mentioned in section 6.1.
- Conditions with high serum iron levels (hemochromatosis, hypersiderosis, chronic hemolysis)
- All forms of anemia in the absence of a confirmed iron deficiency origin. For example, megaloblastic anemia resulting from isolated vitamin B12 deficiency (e.g., an intrinsic factor deficiency), and an isolated folic acid deficiency.
- In case of problems inherent to iron consumption (anemia of lead poisoning, sideroblastic anemia).
- In case of thalassemia.
- In case of degenerative or chronic arthritis.
- In case of conditions requiring frequent and continuous blood transfusions.
- In case of HIV infection without anemia due to iron deficiency highlighted by clinical measures.
- In case of severe liver or kidney problems.

4.4. Special warning and precautions for use

4.4.1. General information

Medical check-ups are required in the following cases.

- Patient with blood disorder,
- Patients suffering from epilepsy,
- Patients having problems of the digestive system or stomach.

- Oral iron preparations are used with caution in patients with gastritis, gastric or intestinal ulcer, Crohn's disease and ulcerative colitis.
- Caution is exercised in cases of chronic alcohol abuse, as it can cause iron overload through increased iron resorption.
- Additional administration of folic acid may be required during hemolytic anemia, chronic infections, anticonvulsive therapies or alcoholism.
- Additional parenteral administration of cyanocobalamin may be necessary for vitamin B12 deficiency.
- A dark coloration of the stools can occur during the treatment with Amifer syrup, however it is not clinically relevant.
- If treatment is ineffective, resulting in an increase in hemoglobin levels of about 0.1g/dL of blood per day (about 2 to 3 g/dL in 3 weeks), treatment should be reviewed.
- In case of anemia associated with an infection or malignant tumor, the iron administered is stored in the reticulo-endothelial system and is used during mobilisation after treatment of the primary condition.

4.4.2. Pediatric population

For infants and children who solemnly need treatment with an iron supplement, sole-ingredient iron syrup (as iron-hydroxide-polymaltose complex), Amifer® Junior, is available.

Accidental administration of iron-containing products can cause fatal toxicity in children under 6 years of age. In the event of an overdose, patients should seek immediate medical attention or a poison control center.

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

Iron resorption can be reduced by simultaneous ingestion of certain food and products rich in phytates, phosphates, tannic acid and calcium.

The concomitant intake of green or black tea may reduce the bioavailability of folic acid.

Simultaneous administration of antacids, phosphates, carbonates, oxalates, calcium and certain antibiotics (tetracyclines) may reduce the effect of iron. Due to possible interaction, it is advisable to allow at least 2 hours between the intake of both medicinal products.

The effect of penicillin, fluoroquinolones, sodium etidronate, sodium clodronate, methotrexate, trimethoprim and pyrimethamine may be antagonised. Due to possible interaction, it is advisable to allow at least 2 hours between the intake of the medicinal products.

Folic acid may increase the metabolism of phenytoin, which could result in lower serum concentrations of phenytoin, especially in patients with folic acid deficiency. In some patients this could lead to an increase in the frequency of epileptic seizures.

4.5.2. Additional information on special populations

No additional information

4.5.3. Pediatric population

No additional information

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

Effects of Amifer syrup on fertility have not been determined.

4.6.2. Pregnancy

Amifer syrup is indicated during pregnancy. See special warnings and precautions for use.

Although no controlled studies of the effects of Amifer syrup in animals or pregnant women are available, the possibility of adverse effects on the foetus seems unlikely.

4.6.3. Lactation

Amifer syrup is indicated during breastfeeding. See special warnings and precautions for use.

It is not known whether ferric ammonium citrate passes into breast milk.

The excretion does not change the mother's iron content and the amount of iron consumed with food. As a result, the administration of formulations of iron to the lactating mother does not cause iron poisoning in the baby and does not eliminate an existing iron deficiency in the baby.

4.7. Effects on the ability to drive and use machines

No known effects.

4.8. Undesirable effects

The table below describes adverse events according to the MedDRA classification. Adverse effects reported from the experience since the introduction of folic acid and iron preparations.

Reported side effects are defined as:very common (≥1/10),

- common (de ≥1/100 à <1/10),
- uncommon (de ≥1/1000 à <1/100),
- rare (de ≥1/10000 à <1/1000),
- very rare (<1/10000),
- not known : cannot be estimated from the available data.

System organ class	Undesirable effect	Frequency
Immune system disorders	Anaphylactic reaction Hypersensibility	Not known
Gastrointestinal disorders	Abdominal disorders Diarrhoea Constipation Dark colouring of the faeces (1) Vomiting	Not known

System organ class	Undesirable effect	Frequency
Skin and subcutaneous tissue disorders	Angioedema (face) Allergic skin reactions such as generalised rash, rash, pruritus, hives, skin edema, photosensitivity reaction	Not known (2)

(1) Dark colouring of the faeces is a well-known side effect of iron-based oral preparations, but is not considered clinically relevant and is often not reported.

(2) Hypersensitivity reactions induced by folic acid have been reported a few times in the literature: anaphylactic reaction, swelling of the face, vomiting and allergic skin reactions (generalised erythema, pruritus, hives).
Iron-based oral preparations are also associated with hypersensitivity reactions such as anaphylactic reactions and allergic skin reactions (rash, pruritus, hives, skin oedema and photosensitivity).

4.9. Overdose

Accidental ingestion occurs mainly in children. Therefore, this preparation must be kept out of the reach of children. In children, the mortality from iron poisoning is important.

Acute intoxication by excessive ingestion may cause necrotic gastroenteritis. Symptoms may appear after 30 minutes. These are abdominal pain, diarrhoea, vomiting of the brown and bloody stomach contents sometimes containing the tablets, dehydration, cyanosis, vertigo, hyperventilation due to acidosis and cardiovascular collapse. In this case, hospitalization is necessary.

In case of acute intoxication with necrotic gastroenteritis it is important to act as quickly as possible:

- Stomach lavage by gastric tube with 1% sodium bicarbonate solution.
- Deferoxamine B: 1 to 2 g intravenously in a 5% dextrose solution.
- Shock, dehydration and acid-base changes should be treated conventionally.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code**:** B03AE01, antianemic, iron preparations, iron in other combinations, iron, vitamin B12 and folic acid

Ferric ammonium citrate

Ferric ion is a component of many enzymes necessary for energy transfer (cytochrome oxidase, xanthine oxidase, and succinic dehydrogenase), and it is also present in compounds necessary for the transfer and use of oxygen (haemoglobin and myoglobin).

Administration of iron preparations corrects erythropoietic abnormalities arising from iron deficiency. Iron also eliminates other iron deficiency symptoms such as tongue sores, dysphagia, nail and skin dystrophy, and cracking of the lips.

Folic acid

In humans, an exogenous source of folic acid is needed for nucleoprotein synthesis and maintenance of normal erythropoiesis. Folic acid is not metabolically active as such, but as a precursor of tetrahydrofolic acid acting as a cofactor for the transfer of 1-carbo reactions in the biosynthesis of purines and thymidylates of nucleic acids. The decreased thymidylate synthesis in patients with folic acid deficiency appears to be responsible for failing DNA synthesis that leads to megaloblastic formation and megaloblastic and macrocytic anaemia.

Cyanocobalamin (vitamin B12)

In humans, an exogenous source of vitamin B12 is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and maintenance of normal erythropoiesis. Cells with rapid division (epithelial cells, myeloid cells, bone marrow cells) seem to require more vitamin B12 intake. Vitamin B12 would be converted to coenzyme B12 in tissues, and this is essential for the conversion of methylmalonate to succinate and the synthesis of methionine from homocysteine, a reaction that also requires folate.

In the absence of coenzyme B12, the regeneration of tetrahydrofolate from its inactive form 5-methyl tetrahydrofolate is impossible, resulting in a functional folate deficiency.

Vitamin B12 would also be needed for the maintenance of reduced sulfhydryl (SH) groups required in several activated SH enzyme systems. Apart from these reactions,

vitamin B12 is also associated with the metabolism of fats and carbohydrates, and with the synthesis of proteins.

Vitamin B12 deficiency leads to megaloblastic anaemia, gastrointestinal damage and neurological damage that begins with an inability to produce myelin, and then follows a gradual degeneration of the axon and nerve head. Parenteral administration of vitamin B12 completely reverses megaloblastic anaemia and gastrointestinal symptoms of vitamin B12 deficiency. The degree of improvement in neurological symptoms depends on the duration and severity of the lesions, although progression of the lesions is immediately stopped.

5.2. Pharmacokinetic properties

Ferric ammonium citrate

Absorption

Iron absorption is very complex and is influenced by several factors including the form in which it is administered, the dose, the iron reserve, the erythroid degree and diet. In healthy subjects, approximately 5-10% of dietary iron is absorbed, and almost 10-30% in iron deficient subjects. It is reported that inorganic iron is absorbed twice as much as dietary iron.

The ferric form Fe^{++} is the most absorbable. Although iron absorption occurs all along the gastrointestinal tract, it is more important in the duodenum, in the proximal portion of the jejunum, and decreases progressively in the distal portion. Some enteric preparations and sustained-release preparations may release iron after the duodenum and proximal jejunum, reducing the absorption of iron.

Distribution

Ferric iron Fe^{++} passes through the lining of the gastrointestinal tract directly into the blood and is immediately linked to the carriers. The β1-globulin transporter transports iron to bone marrow where it is incorporated into haemoglobin. Iron is found in the human body only in a complexed forms with a protein or in the haem-molecules. Approximately 70% iron is found in haemoglobin, 25% as ferritin iron, and haemosiderin, 4% in myoglobin, 0.5% in haem-enzymes and 0.1% in transporters. Iron stores in the form of ferritin and hemosiderin are localized in the liver, the reticuloendothelial system, bone marrow and in the spleen. In women, iron stocks tend to be less than half those of man. In patients with a negative iron balance, the iron stores decrease before the haemoglobin concentration is reduced.

Every day, almost 0.15 - 0.3 mg of iron is excreted in breast milk. Iron is transported through the placenta by the active route because it is against a concentration gradient. The iron requirement for a pregnant woman is between 440 mg and 1.05 g. Every day, iron excretion in a healthy woman, rises only up to 0.5 - 2 mg. This excretion appears mainly as a cellular desquamation such as skin, gastrointestinal mucosa, nails, and hair. Only traces of iron are eliminated in the bile, and sweat. The loss of blood is accompanied by a great loss of iron. Each month, iron loss during normal menstruation amounts to 12 - 30 mg.

Elimination

The large amount of iron emanating from the destruction of haemoglobin is conserved and reused by the body.

Folic acid

Absorption

Folic acid is absorbed rapidly from the gastrointestinal tract after oral administration. Folic acid is mainly absorbed in the proximal portion of the small intestine. Naturally, the folate polyglutamates that appear are hydrolysed in the gastrointestinal tract, into monoglutamate forms of folic acid prior to absorption.
After oral administration, the maximal activity of the folates in the blood is reached in 30 - 60 min. Normal total folate concentrations in serum have been reported, ranging from 0.005 - 0.015 µg / ml. In general, folate serum concentrations below 0.005 µg / ml indicate folate deficiency and concentrations below 0.002 µg / ml are accompanied by megaloblastic anaemia.

Distribution

Tetrahydrofolic acid and its derivatives are distributed in all body tissues; the liver contains almost half of the total serum folate reserves. Folate is actively concentrated in CFS, and normal concentrations of CFS have been reported, ranging from 0.016 to 0.021 µg / ml. Normal erythrocyte folate concentrations vary between 0.175 - 0.316 µg / ml. Folic acid is distributed in the milk.

Elimination

After absorption folic acid is largely methylated in the liver to N5-methyltetrahydrofolic, the main transport and storage form of folate in the body.

After administration of large doses, some folic acid may escape hepatic metabolism, and appear in the blood mainly as folic acid.
After an administration of approximately 2.5 - 5.0 mg, almost 50% of the dose is excreted in the urine. Small doses of folic acid administered orally were found in the stool. Each day, about 0.05 mg of normal body folate storage is eliminated both urinary and faecal as well as by oxidative cleavage of the molecule.

Cyanocobalamin

Absorption
After oral administration, vitamin B12 is irregularly absorbed from the distal portion of the small intestine. Dietary vitamin B12 has a high degree of protein binding, and this binding must be broken down by proteolysis and gastric acid before absorption. In the stomach, free vitamin B12 is linked to the Intrinsic Factor (IF) secreted by the gastric mucosa. This binding is necessary for active absorption of vitamin B12 at the level of the lower ileum. In case of structural or functional damage of the stomach or ileum, the absorption of vitamin B12 is reduced.

After oral administration, the peak plasma is reached only after 8 to 12 hours because vitamin B12 is temporally retained in the wall of the lower ileum. Normal serum concentrations of Vit-B12 are between 200 - 900 µg/ml. In general, serum vitamin B12 concentrations below 200 pg/ml indicate vitally B12 deficiency, and concentrations below 100 pg / ml cause megaloblastic anaemia and / or neurological damage.

Distribution
In intestinal mucosal cells, Vit-B12 is released from the Vit-B12-FI complex and rapidly binds to transport plasma proteins: transcobalamin. Vit B12 is distributed in the liver, bone marrow and other tissues, including the placenta. At birth, the blood vitamin B12 concentration in the newborn is 3 to 5 times higher than in the mother. Vit-B12 is found in breast milk at a concentration approaching that of vitamin B12 in the blood. The total body reserves of Vit-B12 in a healthy individual vary between 1 and 11 mg, of which 50-90% are concentrated in the liver.

Elimination
In healthy subjects receiving only alimentary vitamin B12, almost 3 - 8 µg/ day of Vit-B12 is secreted in the gastrointestinal tract, mainly through the bile with a reabsorption of almost 1 µg. Less than 0.25 µg passes into the urine daily.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Potassium sorbate
- Sodium chloride
- Citric acid
- Orange flavour
- Vanilla flavour
- Mint Flavour
- Sucralose
- Ethanol
- Glycerol
- Ponceau 4R (E124)
- Liquid sorbitol

6.2. Incompatibilities

not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C.

Store in the original package to protect from light .

6.5. Nature and contents of container

Amber coloured glass bottle, closed with a white plastic (polyethylene) screw-cap.

Box with 200ml syrup and a plastic graduated measuring cup.

6.6. Special precautions for disposal and other handlings

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Sofarimex – Indústria Química e Farmacêutica S.A.

Av. das Indústrias – Alto do Colaride

Cacém, 2735-213 Portugal

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

03/2020