ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FERCEFOL® coated tablets
FERCEFOL® syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Coated tablets:
- Ferrous fumarate: 308 mg (equivalent to 100 mg of elemental iron)
- Folic acid: 4 mg
- Vitamin C (ascorbic acid): 200 mg

Syrup:
For 5 ml
- Iron (III) hydroxide polymaltose: 172.4 mg (equivalent to 50 mg of elemental iron)
- Folic acid: 2 mg
- Vitamin C (ascorbic acid): 100 mg

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Curative treatment of iron-deficiency anaemia (4 to 6 months' treatment minimum, combined with an etiological treatment).
- Preventive treatment of iron deficiency in exposed patients: pregnant women, unbalanced diet, (elderly patients, vegetarians, vegans, mental anorexia), untreatable chronic bleedings.
- Megaloblastic anaemia due to folic acid deficiency.
- Chronic intestinal absorption disorders (malabsorption, celiac disease, upper digestive stock).
- Folates intake deficiency: malnutrition, chronic alcoholism.

4.2 Posology and method of administration

Tablets
To be taken preferably before eating, in terms of digestive tolerance, with a glass of water.

Posology:
- Iron-deficiency anaemia:

Adult: 1 tablet per intake, 1 to 2 intakes per day. During 4 to 6 months, combined with an etiological treatment. Either 100 or 200 mg of elemental iron equivalent and 4 to 8 mg of folic acid per day
- Maintenance dose:

Adult: 1 tablet per day.

Children and infants: the syrup formulation is more adapted for children.

Syrup

Adult: 1 to 2 5 ml measures per intake, 1 to 2 intakes per day. During 4 to 6 months minimum combined to an etiological treatment. Either 50 to 200 mg of elemental iron equivalent and 2 to 8 mg of folic acid per day.
Children and infants: the dosage is chosen in terms of the required dose of elemental iron: either 6 to 10 mg/kg/day, 1 to 2 intakes. During 4 to 6 months' au minimum, combined with an etiological treatment.

- Maintenance dose:

Adult: 1 to 2 measures of 5 ml per day.

Method of administration: this medicine is to be taken by oral route.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Iron overload (iron storage disorders, haemochromatosis, chronic haemolysis, hemosiderosis, frequent blood transfusion), iron use disorders (sideroblastic anaemia, lead poisoning anaemia, thalassemia, porphyria cutenea tarda), all non-iron-deficiency anaemia (for example megaloblastic anaemia caused by a deficiency in vitamin B12). Demonstrated intolerance, for instance, during serious inflammatory modifications of the gastro-intestinal tract and peptic ulcer, serious liver and kidney diseases.

4.4 Special warnings and precautions for use

Caution is advised during oral administration of iron-based preparations in patients with inflammatory gastro-intestinal diseases (for example gastritis, gastric or duodenal ulcers, Crohn's disease or haemorrhagic rectocolitis).
In case of delayed gastric emptying, pylorus stenosis and of confirmed presence of diverticula in the gastro-intestinal tract, liquid iron preparations should be preferred over solid dosage forms.
FERCEFOL tablets contains sucrose, FERCEFOL syrup contains sorbitol and glucose syrup; Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When taken simultaneously; iron and tetracyclines absorption is mutually decreased. Antacids, cholestyramine and food decrease the resorption of iron-based products. Iron-based preparations decrease the resorption of penicillamine, gold salts, clodronic acid, etidronic acid and phosphate contained in food.

The simultaneous administration of iron-based preparation with salicylates, phenylbutazone or oxyphenbutazone may induce a reciprocal potentiation of the irritation effects of the gastro-intestinal mucosae.
The simultaneous administration of chloramphenicol may delay the response to siderotherapy.
The simultaneous intake of food items rich in phytates (certain vegetables, cereals), in phosphates (for example eggs), and in tannins (especially tea or coffee) decrease iron resorption, when fish and food items rich in ascorbic acid and in acids contained in fruits increase it.
Folic acid may decrease the effects of folic acid inhibitors taken simultaneously, as aminopterine, tetroxoprime, methotrexate, pyrimethamine, proguanil, triamterene and trimethoprim. Particularly elevated doses of folic acid may decrease the action of antiepileptics/anticonvulsants as for instance carbamazepine, phenytoin, primidone and barbiturates. The needs in folic acid increase during simultaneous administration of long term courses of analgesics, anticonvulsants in general, carbamazepine, hydantoin, oestrogens (contraceptives) and para-aminosalicylic acid.
Antacids containing aluminium or magnesium salts decrease the absorption of folic acid, as cholestyramine and orally administered zinc. Ethanol blocks the absorption of folic acid and stops the enterohepatic cycle. Sulfamides decrease the bacterial synthesis of folic acid; that can result in a folic acid deficiency.

4.6 Fertility, pregnancy and lactation

No controlled study has been carried out in animal or in pregnant woman with FERCEFOL and it is no known if small amounts of iron, passing in the breast milk when the product is administered to the nursing mother, can cause undesirable effects in the infant.
In general, an increased need in iron exists during pregnancy and breastfeeding and damage to the foetus of new-born seem unlikely, given the fact that the product is used to restore a physiological condition during these periods.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Immune system
Rare: hypersensitivity reactions.

Gastrointestinal disorders
Uncommon: repletion feeling, pressure in the upper abdomen, nausea, constipation or diarrhoea.
As all iron-based preparations, FERCEFOL may darken stools. This is cause by the non-resorbed iron and has no impact.

Skin
Rare: allergic reactions with skin rash and pruritus.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 the national reporting system.

4.9 Overdose

In case of acute overdose, the gastrointestinal mucosae damage enables the absorption of significant quantities of unbound iron exercising their toxic systemic effects. Practically, orally route poisoning are very rare and are observed only in young children following accidental intake of high doses. The lethal oral dose of elemental iron is between 200-250 mg/kg of bodyweight. However, fatal outcomes have already been observed with lower doses. Symptoms can occur from 30 to 60 mg/kg. In young children, a total dose of 500 mg can cause life-threatening poisoning.

Oral iron poisoning usually occurs in four phases:

1) 1 to 6 hours following the ingestion: stomach aches, nausea, vomiting, tarry stools, hypotension, dehydration, choc, acidosis, potentially death.
2) An apparent improvement is seen after 4 to 6 hours, and can persist up to 24 hours.
3) Symptoms reappear after 12 to 24 hours with a potentially fatal outcome.
4) Recovery. The delayed damage of acute iron-poisoning may appear after 2 to 6 weeks after the overdose as intestinal occlusion, pylori stenosis and significant scarring of the gastric mucosae.

The treatment of a mild to moderate poisoning consists in giving milk or chicken proteins in order or bind the ferrous ions.
Possibly, provoking vomiting (risk of stomach perforation with a gastric wall that has been damaged) and proceeding to a gastric lavage.
In case of serious poisoning, particularly when serum iron is over the limit of iron binding (around 3.5 mg/l = around 63 µM), it is recommended to administer orally and parenterally the chelating agent deferoxamine as a specific antidote.
When an iron-based preparation has been ingested at potentially fatal doses cannot be eliminated from the gastrointestinal tract by the method mentioned above, an exchange-transfusion and a chirurgical intervention should be considered.

The treatment also consists in treating the choc and in the application of symptomatic measures.
When chronic iron overload, haemochromatosis and hemosiderosis may occur. It usually occurs when the diagnosis of iron-deficiency anaemia was wrong for treatment-resistant anaemia.
No case of acute poisoning either chronic or acute with folic acid has been reported up to date.
Folic acid and vitamin C are relatively non-toxic substances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron in other preparations – various combinations, ATC code: B03AE10

The organism uses iron to incorporate it in haemoglobin, myoglobin and enzymes containing iron. A deficiency in iron can occur when increased needs (for instance pregnancy, growth), increased losses (for instance bleeding) or decreased intake (for instance insufficient iron content of food). An iron-deficiency anaemia occurs mainly after an iron deficiency.
Ferrous fumarate is only progressively dissolved in the stomach and partly in the duodenum. This enables a continuous release of bivalent iron and a good tolerance of the preparation. FERCEFOL also contains vitamin C which helps for the transcellular resorption of iron through the intestinal mucosae and prevents the oxidation of ferrous ions into ferric ions.
Folic acid covers the increased needs in folic acid during pregnancy and breastfeeding.
As all these iron- and acid folic-based preparation, FERCEFOL has no effect on erythropoiesis or on an anaemia that would not be caused by iron or folic acid deficiency.

5.2 Pharmacokinetic properties

Absorption
Iron is mainly absorbed in the duodenum and upper jejunum, and almost exclusively as a bivalent form.
The absorption of iron depends on the needs of the organism. The level of iron resorbed reaches 10 to 20 % of the ingested quantity when there is a deficiency, and 3 to 10 % when there is no deficiency.
The simultaneous intake of food may reduce the resorption of iron by 40-66 %.
The maximal absorption of iron is limited by the capacity of iron transport system. In geriatric patients, the capacity of absorption of iron can be decreased.
Folic acid is almost entirely resorbed. The absorption is essentially at the level of the proximal small intestine.

Distribution
The resorbed iron is bound to a transport protein, transferrin, and transported in the blood to the sites of use as the complex transferrin-iron. The iron which the organism does not need is stored as ferritin (in case of overload, also as hemosiderin) mainly in the cells of the small intestine mucosae, but also in the liver, spleen and bone marrow. Roughly 0.5-1.0 mg of iron pass through in the breastmilk every day. Iron does not cross the placental barrier.

Elimination
The iron released after degradation of haemoglobin is excreted only partially, the majority is reused. Small quantities of iron are eliminated notably by desquamated epithelial cells of the digestive tube and skin, as well as in the faeces, sweat, breast milk, menstrual blood and urine.

5.3 Preclinical safety data

Administration of extreme doses of folic acid to rats results in renal precipitate and urinary flow perturbation.
In the gestating animal, deficit in folic acid or treatment with an antagonist of folic acid have an embryotoxic and teratogenic effect. The effect of acid folic itself has not been subjected to any

toxicological reproduction study. The *in vitro* experimentation carried out with rat embryos has not shown any alteration in the normal embryonal development on very high doses of folic acid.
In the tests performed, folic acid has not shown any mutagenic effect and no carcinogenic effect is known. An increase in the incidence of renal neoplasia induced by a carcinogenic substance has been observed in the rat after administration of massive doses of folic acid subcutaneously.
In animal experimentation, iron salts highly dosed cause gastrointestinal ulceration and liver damage.

Particular remarks
Influence of diagnostic methods:
The serum level of bilirubin may be falsely high; the calcium level may be falsely low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: maize starch, sucrose, purified talc, magnesium stearate, bees wax, colour chocolate supra (E110, E133, E124), gelatine, shellac.

Syrup: xanthan gum, sodium methyl hydroxybenzoate (E219), sodium propyl hydroxybenzoate (E217), sodium benzoate (E221), sorbitol solution, liquid glucose, disodium edetate, saccharin.
Each 5 ml measure contains 1 g of glucose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original container, protected from light and moisture, below 30 °C. Keep out of the sight and reach of children.

6.5 Nature and contents of container

Box of 30 coated tablets packaged in alu-alu strips of 10 tablets.
PET bottle of 150 ml.

6.6 Special precautions for disposal

No special requirements.

5. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

6. MARKETING AUTHORISATION HOLDER

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7. MANUFACTURER

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8. UPDATE DATE

April 2019