FOR THE TREATMENT OF ALL IRON DEFICIENCY RELATED ANEMIAS
Iron is an essential element for living cells, given its ability to gain and lose electrons.

However, excess iron can be toxic because of its capacity to bind electrons to oxygen, thus causing the generation of reactive oxygen species (ROS).

All organisms have developed strategies that allow acquiring, binding and storing elemental iron in an non-toxic, readily available form. Absorption of nearly all dietary Iron (1-2 mg per day) takes place in the proximal duodenum.

Excessive iron absorption results in iron-overload in the parenchymal tissues, while low iron absorption leads to plasma iron deficiency, which manifests itself as hypoferremia (iron deficiency, ID) and iron deficiency anemia (IDA).
ID is the most common nutritional deficiency, affecting about two billion people worldwide. There are three prominent ways to prevent and control the development of ID and IDA: dietary diversification, food fortification and individual supplementation. The preferred treatment of these pathologies is generally the oral administration of iron as ferrous sulfate.

Oral administration, however, can cause many side effects including gastro-intestinal discomfort, nausea, vomiting, diarrhea, constipation and may increase the patient’s susceptibility to infections.
### Description
SIDERAL FORTE® is composed of protected Iron and Vitamin C, useful in case of deficiency or increased requirements. The iron, included in SIDERAL FORTE® is uniquely coated using a liposomal technology that allows the molecule to pass through the stomach, avoiding any gastrointestinal irritation, to be directly absorbed through the lining of the gastrointestinal tract.

### Regulatory Status
Dietary supplement

### Main Ingredients
Liposomal Iron

### Indication
Dietary support for patients being treated with EPO
Enhances serum iron levels for Chronic Kidney Disease and Dialysis patients
Increases the oxygen carrying ability of blood for radiation and chemotherapy patients

### IP
Prior art 2012 estimate expiration 2032
Description: SIDERALFORTE® is a dietary supplement based on protected liposomal Iron, Vitamin C.

Contents Per 100 g Per 1 cps % RDA
Liposomal Iron 5.04 g 30 mg 214.3%
Vitamin C 10,667 g 64 mg 80.0%

Indications and Usage: SIDERAL FORTE® For the treatment of all anemia’s responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence. Useful in treating iron deficiency anemia or increased requirements of Iron and Vitamin C. The iron included in SIDERAL FORTE®, is uniquely coated with liposomal technology that allows the molecule to pass through the stomach, avoiding any gastrointestinal irritation, to be directly through the lining of the gastrointestinal tract.

Dosage: Take one capsule per day with a glass of water.

How Supplied: 20 capsules of 600 mg,

Gluten free Net wt. 12 g
SOLID COMPOSITION COMPRISING IRON FOR USE IN IRON DEFICIENT CONDITIONS

Abstract: The present invention relates to an iron-based composition, for use in conditions of total or relative iron deficiency. In particular, the present invention relates to a solid composition, preferably in the form of powder or granules, for use in the treatment of disorders or diseases related to or derived from an iron deficiency. The composition of the present invention is suitable for pediatric subjects, adolescents, athletes, men, women, pregnant women and elderly. Finally, the present invention relates to a process for preparing said solid composition.
PATENT CLAIMS I:

1. A solid composition for use in the treatment of disorders or diseases related to an iron deficiency comprising or, alternatively, consisting of an iron (III) salt, sucrose esters or sucresters E473 and a lecithin.

2. The composition for use according to claim 1, wherein said composition further comprises a gelatinized or pregelatinized starch.

3. The composition for use according to claims 1 or 2, wherein said iron (III) salt is ferric pyrophosphate; said iron (III) salt is in an amount comprised from 30 to 70%, preferably from 40 to 60% by weight.

4. The composition for use according to claims 1-3, wherein said sucrose esters or sucresters E473 are in an amount comprised from 10 to 30%, preferably from 15 to 25% by weight.

5. The composition for use according to any one of claims 1-4, wherein said lecithin is a lecithin E322 and is selected from the group comprising the maize, sunflower or soya lecithin; said lecithin is in an amount comprised from 0.1 to 1.5, preferably from 0.4 to 1% by weight.

6. The composition for use according to any one of claims 1-5, wherein said sucrose ester or sucrester and said lecithin are in the composition in a weight ratio comprised from 25:1 to 20:1; preferably in a weight ratio comprised from 20:1 to 15:1.

7. The composition for use according to any one of claims 1-6, wherein said gelatinized or pregelatinized starch is selected from the group comprising rice starch or maize starch; said starch is in an amount comprised from 15 to 40%, preferably from 20 to 35% by weight.
PATENT CLAIMS II:

8. The composition for use according to any one of claims 1-7, wherein the iron pyrophosphate is in an amount comprised from 50 to 55% by weight; the sunflower lecithin is in an amount comprised from 0.5 to 0.8 by weight; sucrester E473 is in an amount comprised from 16 to 20% by weight; the gelatinized or pregelatinized rice starch is in an amount comprised from 25 to 30% by weight.

9. The composition for use according to any one of claims 1-8, wherein said solid composition for oral use has a particle size comprised from 8 to 16 microns, preferably from 10 to 14 microns; a bulk density comprised from 0.3 to 0.8 g/ml, preferably from 0.4 to 0.7 g/ml and an iron (III) content comprised from 60 mg/g to 140 mg/g, preferably from 80 mg/g to 120 mg/g, even more preferably from 90 to 110 mg/g.

10. A supplement product or a medical device or a pharmaceutical composition for oral use comprising the solid composition for oral use according to any one of claims 1-9 for use in the treatment of disorders or diseases related to an iron deficiency in pediatric subjects, adolescents, athletes, men, women, pregnant women and elderly.

11. A supplement product or a medical device or a pharmaceutical composition according to claim 10, for use in pediatric subjects, adolescents, athletes, men, women and elderly for preventing anemia and increasing the hemoglobin and ferritin values; or for use in pregnant women for increasing the birth weight of the newborn, preventing maternal anemia and increasing the hemoglobin and ferritin values both during pregnancy and after birth.

12. A supplement product or a medical device or a pharmaceutical composition according to claims 10 and 11, for use in pediatric subjects, adolescents, athletes, men, women and elderly over a period comprised from 1 to 5 months, preferably from 2 to 4 months; or for use in pregnant women to be administered throughout the pregnancy period, in particular from 12th week, until 6 weeks postnatal.

13. A supplement product or a medical device or a pharmaceutical composition according to claims 10-12, for use in pediatric subjects, adolescents, athletes, men, women, pregnant women and elderly, at a dose comprised from 10 to 40 mg of iron (III)/day, preferably from 14 to 30 mg of iron (III)/day, even more preferably 28 mg of iron (III)/day.
Clinical Data

**International publications**
1 paper submitted
2 in “medical writing”
2 new studies (oncology, gastroenterology)
2 new posters (hematology, gastroenterology)

**Oncology, Nephrology, Haematology**
6 published studies vs. ferrous sulfate and I.V. Iron Posters at EU and World Congresses

**International publications**
1 new study (pregnant women)

**Pregnant women**
Study vs. ferrous sulfate
Poster and oral presentations at EU and World Congresses
SAFETY AND EFFICACY OF ORAL LIPOSOMAL IRON SUPPLEMENTED IN ONCOLOGIC PATIENTS WITH CHEMOTHERAPY-RELATED ANEMIA RECEIVING EPOETIN ALFA
National Congress Medical Oncology, Bologna, Italy, November 2011

57 patients, from 39 to 76 years old with chemotherapy–related anemia, treated with chemotherapy, epoetin alfa plus oral liposomal iron

RESULTS
- Significant increase of Hb (Hemoglobin) response (> 2g/dl above baseline)
- Improvement in Quality of Life level/ High tolerability
- None of the patients required red blood cell transfusion
SAFETY AND EFFICACY OF ORAL LIPOSONAL IRON SUPPLEMENTED IN ONCOLOGIC PATIENTS WITH CHEMOTHERAPY-RELATED ANEMIA RECEIVING EPOETIN ALPHA, FINAL DATA
ESMO Congress, Wien, 2012

Total of 72 patients, from 39 to 76 years old with chemotherapy related anemia, treated with chemotherapy, epoetin alpha plus oral liposomal iron 30 mg once daily for 8 weeks.

RESULTS
- Significant increase of Hb (Hemoglobin) response (> 2g/dl above baseline)
- Improvement in Quality of Life level/High tolerability
- None of the patients required red blood cell transfusion

CONCLUSIONS
- Daily supplementation with LI is safe and produces a significant increase in Hb
- This regimen offers an optimal alternative to IV iron supplementation
- LI is the best choice to combine the treatment with EPO
USE OF LIPOSOMAL IRON IN PATIENTS WITH CHRONIC KIDNEY FAILURE AND LOW TOLERABILITY TO FERROUS SULPHATE UNDER CONSERVATIVE TREATMENT
Nephrology and Dialysis units, Benevento and Sant’Andrea (Rome) hospitals

- Evaluation of efficacy and adverse effects in 17 patients affected by kidney failure and using liposomal iron (1 capsule per day) instead of ferrous sulphate
- Evaluation at T0 and T1 (3 months after treatment)
- Parameters: hemoglobin, ferritin, transferrin saturation, sideremia, transferrin

RESULTS
- Significant increase of all parameters (serum iron, ferritin, hemoglobin)
- Liposomal iron therapy is a valid alternative to ferrous sulfate
- No adverse events have been reported in using LI (such as gastro intestinal side effects)
EFFICACY OF ORAL LIPOSOMAL IRON VS INTRAVENOUS IRON FOR THE TREATMENT OF IRON DEFICIT IN PATIENTS WITH CHRONIC KIDNEY DISEASE NOT IN DIALYSIS, PILOT STUDY
University of Naples and Cardarelli Hospital, Campobasso, Italy

Å patients (14 patients treated with liposomal iron and 7 treated with intravenous iron)
Å 8 weeks treatment
Å Primary end-point: evaluation of the hemoglobin increase at the end of the therapy

RESULTS
After 8 weeks treatment anemic patients suffering from chronic renal failure significantly increased their level of hemoglobin vs intravenous iron treated patients, with minor adverse effects
24 patients recruited from June 2008 to December 2010
Randomized study:
- Group A treated with intravenous iron plus erythropoietin alpha
- Group B treated with liposomal iron plus erythropoietin alpha

RESULTS
Therapy with liposomal iron is safe, effective and has demonstrated non-inferiority vs. therapy with intravenous iron (which had minor adverse events, erythema and hypotension)
ERYTHROPOIETIN ALPHA VS BIOSIMILAR ERYTHROPOIETIN ALPHA PLUS LIPOSOMAL IRON AND B12 FOLATES IN PATIENTS WITH REFRACTORY ANEMIA, TWO CENTERS PROSPECTIVE STUDY
Poster presented at International Symposium on Supportive Care in Cancer, New York, June 2012

- 86 patients affected by refractory anemia
- 2 groups, one treated with erythropoietin alpha, one with bio similar erythropoietin alpha
- End Point: verify non inferiority of bio similar erythropoietin in terms of safety, efficacy and costs

RESULTS
Bio similar erythropoietin alpha plus liposomal iron, B12 and folates support appears to be safe, feasible, cost-effective and non inferior to classical erythropoietin alpha support in patients affected by refractory anemia.
Product Positioning

Practice Type

- General Practitioner (GP)
- Gastroenterologist
- Geriatrician
- Surgeon
- Endocrinologist

Indications

- Iron-deficiency anemia (including celiacs)
- Patients undergoing gastrointestinal resection or with G.I. lesions
- Severe blood loss during surgery
Practice Type

Gynecologist
Obstetrician

Indications

Iron deficiency from menstruation or gynecologic problems
Premenstrual Syndrome
Pregnant women
Female athletes
**Practice Type**
- Oncologist
- Hematologist
- Nephrologist
- Radiologist

**Indications**
- Iron-deficiency anemia, (including celiacs)
- Anemia in hematologic patients
- Anemia in oncological patients (from chemotherapy/radiotherapy treatment, neoplastic pathology)
- Patients with cancer-related fatigue
- Nephropathic patients under iron supplementation: conservative treatment or substitution treatment (hemodialysis and pre-dialysis)
- Patients under iron supplementation with Erythropoietin (EPO)
- Patients undergoing gastrointestinal resection or with gastrointestinal tract lesions, causing bleed
- Iron supplementation supporting or substituting iron intravenous therapy
2008 – 2012 SiderAL Portfolio sales show a Compound Annual Growth Rate of 45% (sales performance Italy)
SiderAL sales are 94% of the market increase from 2008 through 2012 (Italy)
SiderAL sells 4 times more than nearest competitor even if is priced 60% above the average market price