HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

28 March 2007

INOFER 100 mg, film-coated tablet
B/100 tablets (CIP: 3352969)

Applicant : LISA-PHARM

ferrous succinate, succinic acid

Date of validated Marketing Authorisation: 2 May 1997

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ferrous succinate, succinic acid

1.2. Indication

- Iron deficiency anaemia.
- Preventive treatment of iron deficiency in pregnant women.

1.3. Dosage

For adults and children above 6 years.

The number of part-doses and the time they are taken should be adapted to the digestive tolerance of the patient.

In order to limit adverse effects, it is advisable to split the dose into several part-doses taken over the course of a day.

- Curative treatment:
  - Adults and children above 30 kg (approximately 10 years old): 100 to 200 mg of metallic iron per day, i.e. 3 to 6 tablets daily.
  - Children from 20 to 30 kg (approximately 6 to 10 years old): 6 to 10 mg of metallic iron per kg per day, i.e. on average 3 to 4 tablets daily.

- Preventive treatment:
  - Pregnant women: 1 to 2 tablets per day, during the last two trimesters of pregnancy (or from the 4th month).

- Duration of treatment:
  - It should be sufficient, normally 3 to 6 months, to correct anaemia and restore iron reserves, which in adults are approximately 1000 mg.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

B	BLOOD AND HEMATOPOIETIC ORGANS
B03	ANTIANAEMIA PREPARATIONS
B03A	IRON PREPARATIONS
B03AA	FERROUS IRON, ORAL PREPARATIONS
B03AA06	Ferrous succinate

2.2. Medicines in the same therapeutic category

Other orally administered iron salts available:

- ASCOFER 33 mg, capsule (ferrous ascorbate)
- FER FERREUX SCHWARZ PHARMA 100 mg, enteric-coated capsule (glycine ferrous sulfate pentahydrate complex)
- FERO-GRAD VITAMINE C 500 (ferrous sulphate)
- FERROSTRANE 0.68%, syrup (iron (sodium feredetate))
- FUMAFER 33 mg/1 g, oral powder (ferrous fumarate)
- FUMAFER 66 mg, tablet (ferrous fumarate)
- TARDYFERON 80 mg, tablet (ferrous sulphate)
- TARDYFERON B9, coated tablet (ferrous sulphate, folic acid)
- TIMOFEROL, capsule (ferrous sulphate – ascorbic acid)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory provided 4 publications[1,2,3,4,] on iron succinate and an extract from the Marketing Authorisation file.

- Meunier[1] recorded a sample of 35 women with severe anaemia (haemoglobin level <10g/100ml) during the second half of pregnancy. These women were treated with one INOFER tablet three times daily for an average of 36 days.
  The following laboratory parameters were corrected: haemoglobin, haematocrit, serum iron and red blood cell count.
- Cardi[2] treated 34 patients with postpartum anaemia (average haemoglobin level < 9.35g/100ml) using INOFER (3 tablets a day) for 2 months in order to correct their anaemia. Efficacy was evaluated using 3 laboratory tests: haemoglobin, haematocrit and serum iron.
  The three parameters were corrected from the first month of treatment.
- Ferraci[3] tested the use of INOFER on a cohort of 49 children aged from 3 months to 8 years (average age 12 months) with iron-deficiency anaemia. This study was not taken into account because, according to the Marketing Authorisation, this medicinal product is only indicated for children over the age of 6 years.

3.2. Adverse effects

The laboratory provided 2 safety studies: the VIGE[5] digestive tolerance study and the COLAU[6] study.

- VIGE: Randomised, comparative study of digestive tolerance of 2 iron salts administered orally to prevent anaemia in pregnant women.

[1] Meunier P. Utilisation d'un nouveau sel de fer dans le traitement des anémies de la grossesse (35 observations), Gaz. Med. de France 1979; 86; 1275-1277.
[2] Cardis S. Essai du succinate ferreux dans le traitement de l'anémie du post-partum. Rev. Franç.Gynecol. 1979; 74 (6): 457-459.
[3] Ferraci J.P. Utilisation d'une nouvelle thérapeutique martiale en pédiatrie. Rev. Internat. Pediatrie 1979; 89: 51-56.
[4] New preparations for oral iron therapy. The Lancet, 1965, October 2, 654-657.
[5] Vigé P., Botto JN., Colau JC. Enquête randomisée comparative de la tolérance digestive de deux sels de fer administrés par voie orale en prévention de l'anémie de la femme enceinte. Reprod. Hum et Hormones, 2006, vol XIX, n°9.

The women included (n=82) were divided into 2 equal groups: one group treated with ferrous sulphate + vitamin B9 (TARDYFERON B9, 1 tablet/day, 50mg of total iron/tablet), and one group treated with ferrous succinate + succinic acid (INOFER, 1 tablet/day, 32.5 mg of total iron/tablet).

The primary endpoint was digestive tolerance on D15 and D30, assessed by interviewing each subject.

A score from 0 (absent) to 3 (significant) was assigned to a list of symptoms: gastric pain/cramps, nausea, vomiting, bloating, constipation and diarrhoea.

At least one adverse effect was reported in 80.5% (33/41) of patients treated with ferrous sulphate (50mg of iron) and in 29.26% (12/41) of patients treated with ferrous succinate (33mg of iron), $p<0.01$.

- COLAU: Retrospective study on ferrous succinate tolerance and compliance during a treatment period of more than 2 weeks.

Twenty-one pregnant and non-pregnant women were included; during interviews they had reported side effects leading them to refuse to take iron treatment orally or to abandon this type of treatment.

Tolerance was assessed on D15 and D28 using a 5-point scale (very good/good/average/poor/stopped).

Results: digestive tolerance was assessed as average by 33.32% (7/21) of patients and good by 52.4% (11/21).

3.3. Conclusion

The efficacy of INOFER has been demonstrated on the basis of limited data. Because of the inadequate quality of the methodology used, the two safety studies do not provide evidence of better tolerance of this medicinal product compared with other orally administered iron salts.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The disorder treated with this medicinal product may be life-threatening either in the immediate term or because of complications.

This medicinal product is a first-line therapy.
This medicinal product is intended as curative or preventive therapy.
The efficacy/safety ratio for this medicinal product is high.

Public health benefit

The public health burden due to iron deficiency anaemia is significant.
Alternative medicinal products exist.
An additional impact on the reduction of iron deficiency-related morbidity compared to use of other iron salts is not expected.
As a result, it is not expected that INOFER will benefit public health.

The actual benefit of this medicinal product is substantial.

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[6] Colau JC. Thérapeutiques martiales, tolérance et observance en gynécologie-obstétrique. Gyn. Obs., n° 502, May 2006, 21-23.

4.2. Improvement in actual benefit

The medicinal product INOFER offers no improvement in actual benefit (IAB V) in relation to comparable medicines.

4.3. Therapeutic use

The recommendations published by ANAES[7] advise treatment of iron deficiency anaemia with iron salts. The recommended treatment time is from 4 to 6 months. These recommendations state that there are no controlled studies comparing the bioavailability and efficacy of different iron salts in anaemic subjects. Preventive treatment of anaemia in pregnant women with isolated iron depletion is administered orally from the 12th week of pregnancy until delivery.

4.4. Target population

The target population consists of patients with iron deficiency anaemia and not just iron deficiency.

According to the SUVIMAX study (1998) conducted on the French population aged 35 to 60, the prevalence of iron deficiency anaemia was 4.4% in women aged 35 to 50, 0.7% in postmenopausal women and 0.4% in men. This implies that approximately 550,000 individuals aged 35 to 60 have iron deficiency anaemia.

This population does not include people under 34 or over 60 years of age. These populations have been estimated using the following hypotheses extrapolated from the data in the "Val de Marne" study[8] (1994):

- Children from 6 to 14 years and men between 14 and 34 years

According to the Val de Marne study, the prevalence of iron deficiency anaemia in men aged 14 to 34 and in children from 6 to 14 is zero. Both of these populations are therefore considered to be marginal.

- Women aged 14 to 34

For women between ages 14 and 34, we have used the hypothesis that the prevalence of iron deficiency anaemia can be extrapolated from that observed in the SUVIMAX study for women aged 35 to 50 (4.4%). This hypothesis is consistent with the results of the "Val de Marne" study. On this basis, 236,000 additional individuals can be assumed to have iron deficiency anaemia.

- Women and men over 60 or 65

In the SUVIMAX study, the prevalence of iron deficiency anaemia among people living in their own homes is extrapolated from that observed in individuals aged 50 to 60, i.e. 0.4% in men and 0.7% in women. This population is therefore estimated at 69,000 individuals.

As the prevalence of iron deficiency anaemia among people over 65 is more frequent if they live in institutions rather than in their own homes, and as this population has not been taken into account in the SUVIMAX and Val de Marne studies, it should be added. The number of individuals over 60 living in institutions who have iron deficiency anaemia has therefore been estimated using the following data and hypotheses:

- number of people over 65 living in institutions: from 500,000 to 550,000.
- anaemia levels in people living in institutions: 25% (E. Pautas, *Anémie du sujet âgé*),
- approximate proportion of anaemia cases in individuals over 70 that is caused by iron deficiency: 75%.

[7] ANAES. Hématologie en pratique courante. Le Concours Médical 1996 (suppl.): 1-54

[8] Epidemiological study conducted on a sample of 1200 individuals chosen at random in the Department.

On the basis of this information, the target population for iron deficiency anaemia in subjects over 65 living in institutions is estimated to be 100,000.

This implies that in total 1,000,000 individuals have iron deficiency anaemia.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance in the indication and at the posology in the Marketing Authorisation.

4.5.1. Packaging: appropriate for the prescription conditions

The Committee points out that in accordance with its decisions on 20 July 2005, it recommends that pack sizes for one-month treatments be harmonised to 30-day packs, and 90-day packs for treatments lasting three months.

4.5.2. Reimbursement rate: 65%