# Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1 NAME OF THE MEDICINAL PRODUCT

Ferrologic 20 mg/ml solution for injection/concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution contains 20 mg iron as iron sucrose [iron(III)-hydroxide sucrose complex].
Each 5 ml ampoule contains 100 mg iron as iron sucrose [iron(III)-hydroxide sucrose complex].

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection/concentrate for solution for infusion.
Ferrologic is a dark brown, non transparent, aqueous solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Ferrologic is indicated for the parenteral treatment of iron deficiency in those cases where oral iron preparations are inadequate.
This can apply to:
- Patients who demonstrated intolerance to oral iron preparations,
- Patients who demonstrated non-compliance with oral iron therapy,
- Conditions where there is a clinical need to deliver iron rapidly to iron stores,
- Patients who insufficiently absorb oral iron preparations (e.g. due to active inflammatory bowel disease).

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. serum ferritin, serum iron, transferrin saturation, haemoglobin, haematocrit, erythrocytic count and hypochromic red cells or red blood cells indices: MCV, MCH, MCHC).

### 4.2 Posology and method of administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Ferrologic.

Ferrologic should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Ferrologic injection (see section 4.4).

Calculation of the required dosage

*Adults and Elderly:*
The total cumulative dose of Ferrologic, equivalent to the total iron deficit (mg), is determined by the haemoglobin level and body weight. The dose and dosage schedule for Ferrologic must be individually estimated for each patient based on a calculation of the total iron deficit:

Total iron deficit [mg] = body weight [kg] x (target Hb - actual Hb) [g/l] x 0.24* + depot iron [mg]

Up to 35 kg body weight: target Hb = 130 g/l respectively depot iron = 15 mg/kg body weight
Above 35 kg body weight: target Hb = 150 g/l respectively depot iron = 500 mg

* Factor = 0.0034 x 0.07 x 1000 (Iron content of haemoglobin 0.34%; Blood volume 7% of body weight; Factor 1000 = conversion from g to mg)

The total amount of Ferrologic required is determined from either the above calculation or the following dosage table (based on a target haemoglobin of 130 g/l for a body weight of ≤ 35 kg and 150 g/l for a body weight of > 35 kg):

| Body weight [kg] | Total numbers of Ferrologic ampoules to be administered: | | | |
|---|---|---|---|---|
| | Hb 60 g/l | Hb 75 g/l | Hb 90 g/l | Hb 105 g/l |
| 30 | 9.5 | 8.5 | 7.5 | 6.5 |
| 35 | 12.5 | 11.5 | 10 | 9 |
| 40 | 13.5 | 12 | 11 | 9.5 |
| 45 | 15 | 13 | 11.5 | 10 |
| 50 | 16 | 14 | 12 | 10.5 |
| 55 | 17 | 15 | 13 | 11 |
| 60 | 18 | 16 | 13.5 | 11.5 |
| 65 | 19 | 16.5 | 14.5 | 12 |
| 70 | 20 | 17.5 | 15 | 12.5 |
| 75 | 21 | 18.5 | 16 | 13 |
| 80 | 22.5 | 19.5 | 16.5 | 13.5 |
| 85 | 23.5 | 20.5 | 17 | 14 |
| 90 | 24.5 | 21.5 | 18 | 14.5 |

To convert Hb (mM) to Hb (g/l), multiply the former by 16.1145.

When the total necessary dose exceeds the maximum daily dose, the administration should be split.
When, after 1-2 weeks, the haematological parameters show no reaction, the initial diagnosis deserves reconsideration.

Calculation of the dosage for replacing blood losses and compensating autologous blood transfusions

*If the amount of blood lost is known:*
The administration of 200 mg of iron (= 2 ampoules of Ferrologic) causes an increase in haemoglobins that is equivalent to one blood unit (= 400 ml with 150 g/l of Hb).

Iron being replaced [mg] = total numbers of blood units lost x 200 or

Number of Ferrologic ampoules required = numbers of blood units lost x 2

*If the haemoglobin value is reduced*:
Use the afore-mentioned formula, considering that the iron deposits do not need to be restored.

Iron being replaced [mg] = body weight [kg] x 0.24 x (ideal Hb – real Hb) [g/l]

e.g.: body weight = 60 kg, Hb deficit = 10 g/l ⇒ amount of iron to be replaced = 150 mg = 1.5 ampoules (= 7.5 ml) of Ferrologic are required.

Posology

*Adults and Elderly:*

The cumulative dose of Ferrologic is to be administered in single doses of 100 mg of iron (one ampoule of Ferrologic) given not more than three times per week depending upon the haemoglobin values. However, if clinical circumstances require rapid delivery of iron to the body iron stores, the dosage schedule may be increased to 200 mg of iron not more than three times per week.
The maximum allowed dose each administration is: 200 mg of iron (two ampoules of Ferrologic) injected during at least 10 minutes or 0.35 ml of Ferrologic/kg of body weight (= 7 mg of iron/kg of body weight), not exceeding 5 ampoules/day (500 mg of iron) diluted in 500 ml of physiological solution and administered by intravenous infusion during at least 3.5 hours once a week.

*Children:*
The use of Ferrologic has not been adequately studied in children and, therefore, Ferrologic is not recommended for use in children.

*Special patient groups:*
It is not known to which extent renal or hepatic dysfunction can influence the pharmacological characteristics of iron (III) hydroxide sucrose complex.

Method of administration:

Ferrologic must only be administered by the intravenous route. This may be by a slow intravenous injection or by an intravenous drip infusion. However, administration by intravenous drip infusion is the preferred route of administration as this may help to reduce the risk of hypotensive episodes and paravenous leakage.. Ferrologic is a strongly alkaline solution (pH 10.5 - 11.1)) and **must never be administered by the subcutaneous or intramuscular route**, nor is it suitable for TDI (total dose infusion) during which the total necessary iron dose equivalent to the iron depletion, is administered on a single occasion.

Ampoules should be visually inspected for sediment and damage before use. Only those with sediment free and homogenous solution must be used. The diluted solution must appear as brown and clear. See also 6.3 shelf-life.

*Intravenous drip infusion:*
Ferrologic must be diluted only in 0.9% sodium chloride solution (normal saline). Each 5 ml ampoule (100 mg iron) of Ferrologic should be diluted in 100 ml of 0.9% saline immediately before infusion (i.e. 2 ampoules in 200 ml, etc. to max. 5 ampoules in 500 ml of normal saline). For stability reasons, dilutions of lower Ferrologic concentrations are not permissible. The solution must be administered at the following rate: 100 ml in at least 15 minutes; 200 ml in at least 30 minutes; 300 ml in at least 1.5 hours; 400 ml in at least 2.5 hours; 500 ml in at least 3.5 hours.

*Intravenous injection:*
Ferrologic may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute (i.e. 5 minutes per ampoule) and not exceeding 2 ampoules Ferrologic (200 mg iron) per injection. After an intravenous injection, extend and elevate the patient’s arm and apply pressure to the injection site for at least 5 minutes to reduce the risk of paravenous leakage.

*Injection into dialyser:*
Ferrologic may be administered during haemodialysis directly into the venous line of the dialyser under the same procedures as those outlined for intravenous administration.

## 4.3 Contraindications

The use of Ferrologic is contra-indicated in cases of:

- hypersensitivity to the active substance, to Ferrologic or any of its excipients listed in section 6.1,
- known serious hypersensitivity to other parenteral iron products.
- anaemia not attributable to iron deficiency,
- iron overload or disturbances in utilisation of iron,
- patients with a history of asthma, eczema or other atopic allergy, because they are more susceptible to

experience allergic reactions,

- pregnancy first trimester**.**

## 4.4 Special warnings and precautions for use

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.
There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Ferrologic should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each Ferrologic injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate
In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron must be used with caution in case of acute or chronic infection. It is recommended that the administration of iron sucrose is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

Hypotensive episodes may occur if the injection is administered too rapidly.

Allergic reactions, sometimes involving arthralgia, have been more commonly observed when the recommended dose is exceeded.

Paravenous leakage must be avoided because leakage of Ferrologic at the injection site may lead to pain, inflammation, tissue necrosis, sterile abscess and brown discoloration of the skin.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

As with all parenteral iron preparations, Ferrologic should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore, oral iron therapy should be started at least 5 days after the last injection of Ferrologic.

## 4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled trials of Ferrologic in pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy and Ferrologic should not be used during pregnancy unless clearly necessary (see section 4.4).

The use of Ferrologic during the first trimester of pregnancy is contraindicated (see section 4.3).
Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Ferrologic should be confined to second and third trimester if the benefit is judged to outweigh the

potential risk for both the mother and the foetus.

Non-metabolised iron sucrose is unlikely to pass into the mother's milk. Therefore, no effects on the suckling child are anticipated. Ferrologic can be used during breast-feeding.

## 4.7 Effects on ability to drive and use machines

In the case of symptoms of dizziness, confusion or light-headedness following the administration of Ferrologic, patients should not drive or use machinery until the symptoms have ceased.

## 4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) of Ferrologic in clinical trials were transient taste perversion, hypotension, fever and shivering, injection site reactions and nausea, occurring in 0.5 to 1.5% of the patients. Non-serious anaphylactoid reactions occurred rarely. In general anaphylactoid reactions are potentially the most serious adverse reactions (see section 4.4). In clinical trials, the following adverse drug reactions have been reported in temporal relationship with the administration of IV iron sucrose, with at least a possible causal relationship:

Within each system organ class, the adverse drug reactions are ranked under the headings of reporting frequency, using the following convention:

| | |
|---|---|
| Very common | (≥1/10) |
| Common | (≥1/100 and <1/10) |
| Uncommon | (≥1/1,000 and <1/100) |
| Rare | (≥1/10,000 and <1/1,000) |
| Very rare | (<1/10,000) |
| Not known | (cannot be estimated from the available data) |

***Nervous system disorders***
Common: transient taste perversions (in particular metallic taste).
Uncommon: headache; dizziness.
Rare: paraesthesia.
Very rare: seizures (in the context of hypersensitivity reactions)

***Cardio-vascular disorders***
Uncommon: hypotension and collapse; hypertension, tachycardia and palpitations.

***Respiratory, thoracic and mediastinal disorders***
Uncommon: bronchospasm, dyspnoea.

***Gastrointestinal disorders***
Uncommon: nausea; vomiting; abdominal pain; diarrhoea.

***Skin and subcutaneous tissue disorders***
Uncommon: pruritus; urticaria; rash, exanthema, erythema.

***Musculoskeletal and connective tissue disorders***
Uncommon: muscle cramps, myalgia.

***General disorders and administration site conditions***
Uncommon: fever, shivering, flushing; chest pain and tightness.
Injection site disorders such as superficial phlebitis, burning, swelling.
Rare anaphylactoid reactions (rarely involving arthralgia); peripheral oedema; fatigue, asthenia; malaise.
Moreover, in spontaneous reports the following adverse reactions have been reported:
Not known: reduced level of consciousness, light-headed feeling, confusion; angio-oedema; and swelling of joints, hyperhidrosis, back pain.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

## 4.9 Overdose

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated, if required, with an iron chelating agent.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron preparations; Iron trivalent, parenteral preparations
ATC-code: B03AC02

The polynuclear iron(III)-hydroxide cores are, at the surface, surrounded by a large number of non-covalently bound sucrose molecules, which results in a complex with a molecular mass of approximately 43 kD. This is sufficiently large to prevent renal elimination. The complex is stable and does, under physiological conditions, not release any ionised iron. The iron in the polynuclear cores is bound in a structure similar to the physiological ferritin. Administration of IV iron sucrose lead to physiological alterations which are accompanied by iron uptake.

## 5.2 Pharmacokinetic properties

***Distribution***
Following intravenous injection of a single dose of Ferrologic containing 100 mg iron in healthy volunteers, maximum iron levels, averaging 538 µmol/l, were obtained 10 minutes after injection. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

***Biotransformation***
The ferrokinetics of IV iron sucrose labelled with $^{59}Fe$ and $^{52}Fe$ were assessed in 5 patients with anaemia and chronic renal failure. Plasma clearance of $^{52}Fe$ was in the range of 60 to 100 minutes. $^{52}Fe$ was distributed to the liver, spleen and bone marrow. At two weeks after administration, the maximum red blood cell utilisation of $^{59}Fe$ ranged from 62% to 97%.

***Elimination***
The iron injected was rapidly cleared from the plasma, the terminal half-life being approx. 6 h. The volume of distribution at steady state was about 8 litres, indicating a low iron distribution in the body fluid. Due to the lower stability of iron sucrose in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This resulted in iron transport of approx. 31 mg iron/24 h.

Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5% of the total body clearance. After 24 hours the plasma levels of iron were reduced to the pre-dose iron level and about 75% of the dosage of sucrose was excreted.

## 5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber that are additional to the information already given in other sections of the SmPC.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Water for injections
Sodium hydroxide

## 6.2 Incompatibilities

**Ferrologic must only be mixed with 0.9% of sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used or added as there is the potential for precipitation and/or interaction.**

## 6.3 Shelf life

2 years.

***Shelf life after first opening the container:***
From a microbiological point of view, the product should be used immediately.

***Shelf life after dilution with 0.9% sodium chloride solution:***
Chemical and physical in-use stability has been demonstrated for 24 hours at 22 ± 2°C. From a microbiological point of view, the diluted product should be used immediately.

## 6.4 Special precautions for storage

Store in original package in order to protect from light. Do not freeze.
For storage conditions of the diluted medicinal product see section 6.3.

## 6.5 Nature and contents of container

5 ml Type I glass ampoule.
Ferrologic is supplied in packs containing 5 ampoules or in multi-packs comprising 10 packs, each containing 5 ampoules. Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

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

## 7 MARKETING AUTHORISATION HOLDER

Fresenius Medical Care Nephrologica Deutschland GmbH
Else-Kröner-Straße 1
Bad Homburg v.d.H. 61352,
Germany

## 8 MARKETING AUTHORISATION NUMBER

PA1350/001/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th April 2008

Date of last renewal: 5th December 2012

## 10 DATE OF REVISION OF THE TEXT

March 2014