SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Niferex 100mg gastro-resistant capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule contains:
Ferrous (II) glycine-sulphate complex 567.7 mg (equivalent to 100 mg Fe^{2+}).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.
Hard gelatine capsule size 0 (approximately 21.7 mm x 7.5 mm) with a chocolate-brown, opaque, unprinted cap and an orange, opaque, unprinted body
Capsule content: grey-brownish, enteric, coated pellets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Iron deficiency.
<[To be completed nationally]> is indicated in adults and children from 6 years (min. 20 kg BW).

4.2 Posology and method of administration

Posology

For all ages, body weights and dosing groups the posology should be adjusted to suit the patient's needs and the response of the clinical variables (e.g. haemoglobin, ferritin and transferrin) should be monitored.
A daily dose of 5mg Fe^{2+}/kg BW should not be exceeded (see section 4.9).

Children from age 6 years (from a body weight of 20 kg), adolescents and adults

Bodyweight (kg)	Capsules per intake	Frequency of intake	Total Fe^{2+} dose (mg)
≥ 20	1	1 time daily	100

Adolescents from age 15 years (from a body weight of 50 kg) and adults

In adolescents from age 15 years and adults the following dosage is recommended at the beginning of therapy in cases of pronounced iron deficiency:

Bodyweight (kg)	Capsules per intake	Frequency of intake	Total Fe^{2+} dose (mg)
50 - < 60	1	2 times daily	200
≥ 60	1	2 - 3 times daily	200 - 300

Elderly patients
No clinical data on the need to adjust the dosage in elderly patients are available (see section 4.4).

Patients with impaired renal or hepatic function
No clinical data on the need to adjust the dosage in patients with impaired renal or hepatic function are available (see section 4.4).

Paediatric population:
X is contraindicated in children aged less than 6 years (see section 4.3).
Children from 6 years (min 20 kg BW) can be given 1 capsule daily.
For further dosages see table.

Method of administration

The capsules should be taken without chewing and with sufficient water. The capsules are to be taken at sufficient intervals from meals (for instance, on an empty stomach in the morning or between two principal meals), because absorption can be reduced by ingredients of food. The duration of therapy is determined according to the laboratory follow-up study results.
If swallowing of the capsule proves difficult or is not desirable, the capsule content can also be taken without the capsule body. Therefore the patient cautiously draws the capsule body over a spoon, in which the granules are gathered. After the granules have been taken from the spoon, the patient should drink sufficient water.
The treatment should be continued until normal values have been obtained. The treatment can be continued as long as necessary to replenish the body iron stores.
Treatment duration varies depending on the severity of the deficiency, but generally about 10 to 20 weeks treatment is required, or longer in case of persisting underlying pathology. Treatment duration in prevention of iron deficiency varies depending on the situation (pregnancy, blood donation, chronic haemodialysis and planned autologous transfusion).

4.3 Contraindications

- Esophageal stricture
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Repeated blood transfusion.
- Haemochromatosis, chronic haemolysis with signs of iron accumulation, sideroblastic anaemia, lead anaemia, thalassaemia and forms of anaemia secondary to other haemoglobinopathies.
- Children below age 6 years.
- Children 6 years and older weighing < 20 kg.

4.4 Special warnings and precautions for use

- Patients with existing gastrointestinal disease such as inflammatory bowel disease, intestinal stricture, diverticulae, gastritis, stomach and intestinal ulcers should be treated carefully with Ferrous(II)-glycine-sulphate complex.
- Patients with severe and chronic renal disease who require erythropoietin, should be treated carefully and iron should be given intravenously as oral iron is poorly absorbed in uraemic individuals.
- Elderly people presenting with blood or iron loss of unknown origin have to be carefully examined for the cause of anaemia / the source of haemorrhage before treatment with Ferrous(II)-glycine-sulphate complex.
- Patients with impaired hepatic function and patients suffering from alcoholism should be treated carefully with Ferrous(II)-glycine-sulphate complex.
- In children especially, iron preparations may cause poisoning.
- Tooth discoloration may occur during ferrous(II)-glycine-sulphate complex therapy. According to the scientific literature, this tooth discoloration can either regress spontaneously after

discontinuation of the medicinal product, or has to be removed by abrasive toothpaste or by professional dental cleaning.

- This medicine contains less than 1 mmol sodium (23 mg) per 1 capsule, that is to say essentially‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations should be avoided

Intravenous administration of iron salts
Administration of iron intravenously concomitantly with oral administration of iron may induce hypotension or even collapse due to the fast release of iron due to saturation of transferrin. The combination is not recommended.

Doxycycline:
Orally administered iron salts inhibit the absorption and the enterohepatic circulation of doxycycline. The combination should be avoided.

The following combinations may require dose adoption:

Iron inhibits the absorption of a many medicinal products by chelation. The interval between the administration of X and the medicinal products mentioned below should therefore be as long as possible.

Fluoroquinolones:
When iron salts are coadministered with fluoroquinolones, the absorption of the latter is significantely impaired. The absorption of norfloxacin, levofloxacin, ciprofloxacin, gatifloxacin and ofloxacin is inhibited by iron between 30 and 90%. Fluoroquinolones should be administered at least 2 h before or at least 4 h after X.

Methyldopa (L-form):
When ferrous sulphate was given at the same time, or 1 h or 2 h before the methyldopa, the bioavailability of methyldopa was reduced 83%, 55% and 42% respectively. The interval between the administrations of these compounds should be as long as possible.

Thyroid hormones:
When coadministered the absorption of thyroxine is inhibited by iron, which can affect the result of the treatment. The interval between the administrations of the compounds should be at least two hours.

Tetracyclines:
When iron is coadministered orally with tetracycline (e.g. doxycycline), both the absorption of iron and the absorption of the tetracyclines are inhibited. The interval between the administration of X and tetracyclines other than doxycycline should be at least three hours.

Penicillamine:
The absorption of penicillamine is reduced, as it may form chelates with iron. Penicillamine should be administered at least 2 h before X.

Bisphosphonates:
Medicinal products containing iron form complexes with *Bisphosphonates in vitro.* When iron salts are coadministered with *Bisphosphonates*, the absorption of *Bisphosphonates* may be impaired. The time-interval between the administration of these medicinal products should be at least two hours.

Levodopa:

The simultaneous administration of iron sulphate and levodopa to healthy volunteers reduces the bioavailability of levodopa by 50%. The bioavailability of carbidopa is also reduced (75%). The interval between the administrations of these compounds should be as long as possible.

Nonsteroidal anti-inflammatory agents:
Concomitant administration of iron salts with non-steroidal anti-inflammatory agents may intensify the irritant effect on the gastrointestinal mucosa.

Antacids:
Antacids containing oxides, hydroxides or salts of magnesium, aluminium and calcium chelate iron salts. The interval between the administrations of these two compound groups should therefore be as long as possible, the minimum time is two hours between the administrations of the antacid and iron.

Calcium:
The concomitant use of iron and calcium decreases the absorption of iron. X should be taken apart from calcium-containing food and beverages.

Bioavailability of X could be reduced by iron complexing agents (such as phosphates, phytates and oxalates) contained in vegetable food and constituents of milk, coffee and tea. The interval between the administration of these compounds should be at least two hours.

Administration of ferrous (II)-glycine-sulphate complex may lead to a false positive blood stool test.

Others:
Treatment with ferrous glycine sulphate containing vitamin C can potentially result in false negative guaiac-based test results. When iron is administered orally, a dark coloration of the faeces, not resulting from occult gastrointestinal haemorrhage, may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryo/foetal development or postnatal development (see section 5.3).
Data collected on exposed pregnancies indicate no adverse effect on pregnancy, parturition or on the health of the foetus/new-born child.
X could be considered when a risk for iron deficiency is confirmed.

Lactation
With supplementation, iron excretion in the breast milk is approximately 0.25 mg/day during normal lactation.
There are no studies on possible adverse effects of iron in breastfed newborns of treated mothers.
Therefore, the use of X could be considered during lactation, when needed.

Fertility
There are no fertility data available from the use of ferrous(II)-glycine-sulphate complex in human.

4.7 Effects on ability to drive and use machines

X has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects frequencies are defined as: very common (≥1/10),

common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100),
rare (≥1/10,000, <1/1,000) very rare (<1/10000), ´not known' (cannot be estimated from the available data

During administration of Ferrous glycine sulphate the following undesirable effects may be observed:

Gastrointestinal disorders:
Common: Abdominal discomfort, heartburn, vomiting, diarrhoea, nausea, constipation, and dark coloured faeces.

Rare: Tooth discoloration (see also section 4.4 Special warnings and special precautions for use).

Not known: Abdominal pain and abdominal pain upper, gastrointestinal haemorrhage, tongue discolouration, oral mucosal discolouration.

Skin and subcutaneous tissue disorders:
Rare: Hypersensitivity reactions of the skin, e.g. exanthema, rash and urticaria.

Immune system disorders:
Not known: Anaphylactic reaction

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 listed in Appendix V.

4.9 Overdose

Symptoms of intoxication may appear after dosages as 20 mg Fe^{2+}/ kg BW or more. The appearance of serious toxic effects must be anticipated for dosages from 60 mg Fe^{2+} /kg BW and more. Intoxications by dosages of 200 to 400 mg Fe^{2+}/kg BW result in death when left untreated.

Paediatric population
A total dose as small as 400 mg Fe^{2+} may lead to life-threatening states in infants.

Iron poisoning can show several phases. During the first phase, about 30 minutes to 5 hours following oral administration, symptoms such as restlessness, stomachache, nausea, vomiting and diarrhoea are observed. The faeces show a tarry coloration, the vomit can contain blood. Shock, metabolic changes such as too much acid in the body and coma can develop. This is often followed by a phase of apparent recovery that may last up to 24 hours. Then diarrhoea, shock and acidosis reappear. Death can occur after convulsions, Cheyne-Stokes breathing, coma and pulmonary oedema.

Therapeutic measures for overdose:

Gastric lavage or causing vomiting may be considered shortly after overdose. A specific antidote is desferrioxamine (Desferal®).
For detailed information please see corresponding information of the manufacturer.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-anemic, ATC code: B03AA01

Iron is essential for transport of oxygen (e.g. haemoglobin) and for energy transfer in the body. The content of iron in the body is about 50 mg of Fe^{2+}/kg BW in men and about 38 mg of Fe^{2+}/kg BW in women.

Mechanism of action
Iron in the ferrous form (Fe^{2+}) is the bioavailable form which can enter the cell metabolism along with the existing heme iron. Complexed mainly with amino acids, iron is transported into the mucosal epithelial cells of the small intestine, mainly in the duodenum and to a lesser extent in the proximal jejunum. There the larger quantity of iron from nonheme food sources is reduced to the ferrous form (Fe^{2+}). The iron derived from X is already in the reduced ferrous form (Fe^{2+}) and hence readily bioavailable for absorption into the cell metabolism.

Pharmacodynamic effects
Iron is necessary to the organism to build up hemoglobin, myoglobin and enzymes containing ferrous. Iron deficiency may be triggered by a higher demand of iron (e.g. during growth and pregnancy), a higher iron loss (e.g. bleeding) or decreased iron intake (e.g. insufficient content of iron in the food). An iron deficiency anemia may occur as a consequence of an iron deficiency.

X is a medicinal product for the treatment of iron deficiency. It contains iron (Fe^{2+}) in a form that the body can easily absorb and utilize. The product is therefore suitable to eliminate symptoms caused by iron deficiency. Like all iron preparations, X has no effects on erythropoiesis or anaemia that is not due to iron deficiency.

Paediatric population
See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
X, hard capsules contain gastro-resistant granules. The capsule shell dissolves in the stomach and the acid-resistant coated pellets reach subsequently, and in small amounts, the duodenum where they dissolve and release the iron complex.

Bioavailability
In patients with depleted iron stores the relative bioavailability is 95 % that of an aqueous iron sulphate solution as reference. This is equivalent to a Fe2+ absorption in the range of 15 %.

Distribution
In the blood, iron irons are bound to transferrin and transported to sites where they are needed. Iron is stored as ferritin in the liver, spleen and bone marrow.

Elimination
Only a small portion (1 – 2 mg/day) of the iron released by the breakdown of haemoglobin (20 – 30 mg a day) is excreted in the faeces. Most is re-used by the body, mainly for the synthesis of haemoglobin.

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

Ascorbic acid, cellulose microcrystalline, hypromellose, hydroxypropylcellulose, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (Eudragit L30 D-55) (contains methacrylic acid-ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80), acetyltriethyl citrate, talc

capsule shell:
-body: gelatin, titanium dioxide (E 171), red iron oxide (E 172), yellow iron oxide (E 172)
-cap: gelatin, titanium dioxide (E 171), red iron oxide (E 172), black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Blister of paper/aluminium composite film with a polypropylene (PP) white opaque foil with 30, 50, 90, 100 and 500x1 gastro-resistant capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8 MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10 DATE OF REVISION OF THE TEXT

28 April 2023