Summary of Product Characteristics

1. Name of the medicinal product
Xeratec 100mg/5ml Solution for IV Injection.

2. Qualitative and quantitative composition
Vial contains 100 mg of Iron Sucrose as active substance.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Brown to Red-Brown Solution for intravenous injection.

4. Clinical particulars
4.1.Therapeutic indications
Iron deficiency in patients in whom oral iron therapy is not sufficiently effective or not feasible. such as:
- Intolerance to oral iron preparations.
- Inflammatory gastrointestinal disorders (e.g. ulcerative colitis) which may be aggravated by oral iron therapy.
- Treatment-refractory iron deficiency states where unreliability in taking oral iron preparations is suspected.

Xeratec should only be administered where the indication is confirmed by appropriate investigations. Suitable laboratory analyses are haemoglobin. serum ferritin. transferrin saturation.Administration of **Xeratec** to children below 3 years of age is not recommended due to lack of experience.

4.2.Posology and method of administration
Xeratec may only be administered slowly via the intravenous route.
Xeratec must NOT be administered subcutaneously or intramuscularly.
During and after each administration of **Xeratec**, patients must be carefully monitored for signs or symptoms of hypersensitivity reactions. Provision of appropriate emergency treatment must be assured.

The cumulative dose of **Xeratec** must be calculated for each patient individually and must not beexceeded. The dose is calculated on the basis of body weight and Hb value.
If the required total dose exceeds the maximum permissible single dose of 200 mg (injection) or 500 mg (infusion), then the administration of the total dose must be divided.

Calculating the dose
The total cumulative dose of **Xeratec**, equivalent to the total iron deficit (mg), is determined by the haemoglobin level (Hb) and body weight (BW). The dose of **Xeratec** must be individually calculated for each patient according to the total iron deficit calculated with the following Ganzoni formula:
- Total iron deficit [mg] = [BW [kg] x (target Hb - actual Hb) [g/dl] x 2.4*] + storage iron [mg]
- Less than 35 kg BW: target Hb = 13 g/dl and storage iron = 15 mg/kg BW
- 35 kg BW and above: target Hb = 15 g/dl and storage iron = 500 mg
- Factor 2.4 = 0.0034 (iron content of Hb = 0.34%) (0.07 (blood volume = 7% of BW) x 1000 (conversion of [9] to [mg]) x 10

Total **Xeratec** to be administered (in ml) = Total iron deficit [mg] */20* mg iron/ml

Total amount of **Xeratec** (ml) to be administered according to body weight and actual Hb level:

BW	**Total amount of Xeratec (20 mg iron per ml) to be administered**			
	Hb 6.0 g/dl	Hb 7.5 g/dl	Hb 9.0 g/dl	Hb 10.5 g/dl
10 kg	15.0 ml	15.0 ml	12.5 ml	10.0 ml
15 kg	25.0 ml	22.5 ml	17.5 ml	15.0 ml
20 kg	32.5 ml	27.5 ml	25.0 ml	20.0 ml
25 kg	40.0 ml	35.0 ml	30.0 ml	27.5 ml
30 kg	47.5 ml	42.5 ml	37.5 ml	32.5 ml
35 kg	62.5 ml	57.5 ml	50.0 ml	45.0 ml
40 kg	67.5 ml	60.0 ml	55.0 ml	47.5 ml
45 kg	75.0 ml	65.0 ml	57.5 ml	50.0 ml
50 kg	80.0 ml	70.0 ml	60.0 ml	52.5 ml
55 kg	85.0 ml	75.0 ml	65.0 ml	55.0 ml
60 kg	90.0 ml	80.0 ml	67.5 ml	57.5 ml
65 kg	95.0 ml	82.5 ml	72.5 ml	60.0 ml
70 kg	100.0 ml	87.5 ml	75.0 ml	62.5 ml
75 kg	105.0 ml	92.5 ml	80.0 ml	65.0 ml
80 kg	112.5 ml	97.5 ml	82.5 ml	67.5 ml
85 kg	117.5 ml	102.5 ml	85.0 ml	70.0 ml
90 kg	122.5 ml	107.5 ml	90.0 ml	72.5 ml

Target Hb value
Below 35 kg BW:
Target Hb = 13 g/dl 35 kg BW and above:

Target Hb = 15 g/dl
To convert Hb (mM) to Hb (g/dl), multiply the former by 1.6.

If the required total dose exceeds the maximum permissible single dose of 200 mg (injection) or 500 mg (infusion), then the administration of the total dose must be divided.

Normal posology
Adults: 5 - 10 ml of **Xeratec** (100 - 200 mg iron) one to three times a week. For administration time and dilution ratio see "Administration".
Children above 3 *years* of *age:* There is a limited amount of data in children under study conditions. If there is a clinical need, it is recommended not to exceed 0.15 ml of **Xeratec** (3 mg iron) per kg body weight not more than three times per week. For administration time and dilution ratio, see under "Administration".

Maximum tolerated single and weekly dose

Adults
As an injection, maximum tolerated dose per day given not more than 3 *times per week:*

- 10 ml of **Xeratec** (200 mg iron) injected over at least 10 minutes.

As an infusion, maximum tolerated dose per day given not more than once per week:
- Patients above 70 kg body weight: 500 mg iron (25 ml of **Xeratec**) over at least 3 1/2 hours
- Patients of 70 kg body weight and below: 7 mg iron/kg body weight over at least 3 1/2 hours

The infusion times specified in the "Administration" section must be strictly adhered to, even if the patient does not receive the maximum tolerated single dose.

If the treatment is not successful (increase in hemoglobin of approx. 0.1 g/dl of blood/day and approx. 1.0 - 2.0 g/dl after 1 - 2 weeks), the original diagnosis needs to be reviewed and any persistent blood loss ruled out.

Administration
Xeratec must only be administered intravenously by drip infusion, by slow injection or directly into the venous line of the dialysis machine.
Xeratec must not be administered intramuscularly or subcutaneously.
If the required total dose exceeds the maximum permissible single dose, then the administration of the total dose must be divided.

Intravenous drip infusion
Xeratec must only be diluted in sterile 0.9% m/v sodium chloride (NaCl) solution.
Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Xeratec dose (mg of iron)	Xeratec dose (ml of Xeratec)	Maximum dilution volume of sterile 0.9% m/V NaCl solution	Minimum Infusion Time
50 mg	2.5 ml	50 ml	8 minutes
100 mg	5 ml	100 ml	15 minutes
200 mg	10 ml	200 ml	30 minutes
300 mg	15 ml	300 ml	1.5 hours
400 mg	20 ml	400 ml	2.5 hours
500 mg	25 ml	500 ml	3.5 hours

Intravenous injection
Xeratec may be administered by slow intravenous injection at a rate of 1 ml undiluted solution perminute and not exceeding 10 ml (200 mg iron) per injection.

The patient's arm is to be stretched after injection. Paravenous leakage must be avoided, as theleakage of **Xeratec** at the injection site may lead to pain, inflammation, tissue necrosis and potentially prolonged brown discoloration of the skin.

Injection into venous line of *the dialysis machine*
Xeratec may be administered during a haemodialysis session directly into the venous line of thedialysis machine under the same conditions as for intravenous injection.

4.3.Contraindications
- Known hypersensitivity to the active substance or any of the excipients according to the composition.
- Anaemia not caused by iron deficiency (e.g. haemolytic anaemia, megaloblastic anaemia due toVitamin B12 deficiency, disorders of erythropoiesis, bone marrow hypoplasia, lead anaemia).
- Evidence of iron overload (haemochromatosis, haemosiderosis) or hereditary disturbances in utilisation of iron (sidero-achrestic anaemia, thalassaemia, porphyria cutanea tarda).
- The first trimester of pregnancy.

4.4.Special warnings and precautions for use

The intravenous administration of parenteral iron products can cause immediate-type acute hypersensitivity reactions (anaphylactoid/anaphylactic reactions), which may be fatal.

Such reactions have been reported even where previous administrations of parenteral iron products have been tolerated without complications. In the case of patients who have had hypersensitivity reactions to iron dextran, **Xeratec** may only be administered in compelling situations and under strict precautionary measures.

Treatment with **Xeratec** should be prescribed by the attendant physician only after carefully determining the indication.

• **Xeratec** should only be used if healthcare professionals who can assess and treat anaphylactic reactions are immediately available as well as only in an institution in which all facilities for resuscitation are available. Before each administration of **Xeratec**, patients should be actively questioned about previous undesirable effects from intravenous iron products.

Typical symptoms of acute hypersensitivity reactions are: fall in blood pressure, tachycardia (and even anaphylactic shock), respiratory symptoms (including bronchospasm, laryngeal and pharyngeal oedema), abdominal symptoms (including abdominal cramps, vomiting) or skin symptoms (including urticaria, erythema, pruritus).

Patients should be carefully monitored for any signs and symptoms of a hypersensitivity reaction during and for at least 30 minutes after the administration of parenteral iron products. Should allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

Adrenaline, e.g. in doses of 0.3 mg intramuscularly, is recommended in the first instance for the emergency drug treatment of acute anaphylactic/anaphylactoid reactions, and only after this antihistamines and/or corticosteroids (later onset of action).

The risk of hypersensitivity reactions is increased in patients with known allergies including drug intolerance, a history of severe asthma, eczema and other forms of atopy, and also in patients with immunological or inflammatory disorders. (e.g. systemic lupus erythematosus, rheumatoid arthritis).

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. Careful monitoring of iron status is recommended to avoid iron overload.

In patients with elevated ferritin level parenteral iron may have an unfavorable effect on the courseof a bacterial or viral infection.

Parenteral iron should be used with caution in the case of acute or chronic infection.
In patients with chronic infection, a risk/benefit evaluation should be performed. It is recommended that the administration of **Xeratec** is stopped in patients with bacteraemia.

Paravenous leakage must be avoided, as the leakage of **Xeratec** at the injection site can lead to pain, inflammation, tissue necrosis and potentially prolonged brown discoloration of the skin. If this occurs, the administration of **Xeratec** must be stopped immediately.

A drop in blood pressure is commonly observed in association with the intravenous administrationof iron. Therefore, the infusion should be administered with caution.
Particular caution with the administration of **Xeratec** is needed in patients with hepatic impairment, decompensated cirrhosis of the liver, epidemic hepatitis, Osler-Rendu-Weber syndrome, infectious kidney disorders in the acute phase, uncontrolled hyperparathyroidism.

4.5.Interaction with other medicinal products and other forms of interaction
Xeratec is only indicated if oral iron therapy cannot be implemented or is not adequately effective. In this last case, it is not recommended to administer **Xeratec** at the same time as oral ironpreparations, as the absorption of orally administered iron may be reduced.

4.6.pregnancy and lactation
There is insufficient data from the use of iron sucrose in pregnant women in the first trimester. Data from the use of iron sucrose injections in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn.

It is so far unknown whether the iron (III) hydroxide sucrose complex, which is present in **Xeratec**, crosses the placenta. Transferrin-bound iron does cross the placental barrier; lactoferrin-bound iron passes into breast milk.

There are no investigations on the influence on iron levels in newborns.
Xeratec is contraindicated during the first trimester of pregnancy and may only be used during the2nd and 3rd trimester if strictly indicated.

A careful risk/benefit assessment is necessary before administration during pregnancy since hypersensitivity reactions may result in a particular risk to the mother and child.

Body weight before the onset of pregnancy should be used to calculate the required quantity of iron, to avoid a potential overdose.

There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose, therefore the risk/benefit should be assessed.

4.7.Effects on ability to drive and use machines
No corresponding studies have been carried out. **Xeratec** is unlikely to influence the ability to drive or use machines. However, if symptoms such as dizziness, confusion or light-headedness occur following the administration of **Xeratec**, affected patients should not drive a car or use machines until the symptoms have abated

4.8.Undesirable effects
The most common adverse drug reaction (ADR) with Xeratec is dysgeusia. Other common undesirableeffects included nausea, hypotension, hypertension and infusion site pain.

The most important serious adverse drug reactions associated with Xeratec are hypersensitivity reactions. Hypersensitivity reactions of an immediate nature (anaphylactoid /anaphylactic reactions) are rare.

In general, anaphylactoid! anaphylactic reactions are very serious adverse effects which can be fatal. Symptoms include, among others, circulatory collapse, hypotension, tachycardia, respiratory symptoms (bronchospasm, larynx and pharynx angioedema, etc.), abdominal symptoms (abdominal pain, vomiting, etc.), and skin symptoms (urticaria, erythema, pruritus etc.).

The following adverse reactions were reported in temporal relationship with the administration ofiron sucrose injection, whereby a causal relationship may be assumed. The frequency of the below adverse drug reactions is classified as common *«1/10,* ~1/100), uncommon *«1/100,* ~1/1000) and rare

«1/1000, ~1/10000).
Infections and InfestationsRare: Pneumonia.
Blood and lymphatic system disordersUncommon: Polycythemia (1).
Immune system disorders
Uncommon: Hypersensitivity reactions.*Metabolism and nutrition disorders Rare:* Iron overload.
Nervous system Common: Dysgeusia.
Uncommon: Headache, dizziness, burning sensation, paraesthesia, hypoaesthesia.
Rare: Syncope, migraine, somnolence.

Cardiac disorders
Common: Hypotension and collapse, tachycardia.
Rare: Palpitations.
Vascular disorders
Common: Hypotension, hypertension. *Uncommon:* Thrombophlebitis, phlebitis.*Rare:* Flushing.
Respiratory organs Uncommon: Dyspnoea. *Renal and urinary disorders Uncommon:* Chromaturia. *Gastrointestinal disorders Common: Nausea.*
Uncommon: Vomiting, abdominal pain, diarrhea, constipation.
Rare: Dry mouth.
Skin and subcutaneous tissue disordersUncommon: Pruritus, rash.
Musculoskeletal system

Uncommon: Muscle cramps, myalgia, arthralgia, pain in extremity, back pain.
Rare: Limb discomfort, muscle spasms.
General disorders and administration site conditionsCommon: Injection site pain.
Uncommon: Chills, asthenia, fatigue, pain, injection site reactions, injection site irritation, injection site extravasation, injection site discoloration, injection site burning, injection site swelling.
Rare: Feeling hot, chest pain, pyrexia, injection site pruritus, injection site bruising.
Investigations
Uncommon: Gamma-glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function tests abnormal.
Rare: Serum ferritin increased1), blood creatinine increased, blood lactate dehydrogenase increased.

1) Possibly as a consequence of iron overdose or iron overload

4.9.Overdose

Overdose can cause iron overload, which may manifest itself as haemosiderosis. Overdose should be treated, as deemed necessary by the treating physician, with an iron chelating agent or according to standard medical practice

5. Pharmacological properties

5.1.Pharmacodynamics properties

Mechanism of action

Following intravenous administration, Iron Sucrose is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

5.2.Pharmacokinetic properties

N.A

5.3.Preclinical safety data

Limited preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. genotoxicity and toxicity to reproduction and development.

In embryo-fetal toxicity studies using iron replete animals. iron sucrose was associated with minor skeletal abnormalities in the rat foetus at dosages that caused maternal toxicity.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child.

In lactating rats treated with 59Fe-labelled iron sucrose. low secretion of iron into the milk and transfer of iron into the offspring was observed. Non metabolized iron sucrose is unlikely to pass into the mother's milk.

6. Pharmaceutical particulars

6.1.List of excipients

Sodium Hydroxide, Water for Injection.

6.2.Incompatibilities

Xeratec must only be mixed with sterile 0.9% *(mN)* NaCl solution under aseptic conditions. There is the potential for precipitation and/or interaction if mixed with other solutions or medicinal products. The compatibility with containers other than glass, polyethylene and PVC is not known.

6.3.Shelf life

2 years

6.4.Special precautions for storage

Do not store above 30°C, protect from light. The Xeratec solution must not be frozen orexposed to extreme heat.

6.5.Nature and contents of container

Clear Tubular Glass Vial 6R Type I with Rubber Stopper 20 mm.

6.6.Special precautions for disposal and other handling

Before use, the vials should be visually inspected for sediments and damage. Use only those containing a homogeneous and sediment-free solution.

Once opened, the vials must be used immediately. The dilute solutions prepared with sterile 0.9%*(mN)* NaCl solution must be administered as soon as possible for microbiological reasons. They must not be stored above 30°C and must be administered within 12 hours.

7. Marketing authorization holder

MS Pharma – Jordan
King Abdullah (II) Bin Al-Hussein Industrial Estate, Amman JordanTelephone +962 6 40 20 680
Fax: +962 6 40 20 679

8. Marketing Authorisation Number(S)

TAN 22 HM 0031

9. Date of First Authorisation/Renewal of The Authorisation

10/01/2022

10. Date of Revision of the Text