NOVARTIS

Drug Regulatory Affairs

DESFERAL®

(desferrioxamine)

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

DESFERAL®

2 Qualitative and quantitative composition

Active substance: N-[5-(3-[(5-aminopentyl)-hydroxycarbamoyl]-propionamido)pentyl]-3-([5-(N-hydroxyacetamido)-pentyl]-carbamoyl)-propionohydroxamic acid monomethane sulphonate (= desferrioxamine methane sulphonate). One vial contains 500 mg or 2 g desferrioxamine methane sulphonate.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Vials containing 500 mg or 2 g dry active substance for injection.

Information might differ in some countries.

4 Clinical particulars

4.1 Indications

Therapeutic

Monotherapy iron chelation treatment for chronic iron overload, e.g.

- transfusional haemosiderosis, as seen in thalassaemia major, sideroblastic anaemia, auto-immune haemolytic anaemia, and other chronic anaemias [48,52-55,94,158-160].
- idiopathic (primary) haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, cardiac disease, hypoproteinaemia) preclude phlebotomy [56,57].
- iron overload associated with porphyria cutanea tarda in patients unable to tolerate phlebotomy [58-60,161-164,184].

Treatment for acute iron poisoning [61,62,93,97,104].

Treatment for chronic aluminium overload in patients with end-stage renal failure (under maintenance dialysis) [63-73,89,90,100,102] with

- aluminium-related bone disease,
- dialysis encephalopathy or
- aluminium-related anaemia.

Diagnostic

Diagnosis of iron or aluminium overload [8,9,74,98,100,102].

4.2 Posology and method of administration

Treatment for chronic iron overload

The main aim of chelation therapy in iron overload in young patients is to achieve an iron balance and to prevent haemosiderosis, while in the older patient a negative iron balance is desirable in order to reduce slowly the increased iron stores and to prevent the toxic effects of iron [48,53,159].

Children and adults

It is recommended that therapy with Desferal® be started after the first 10 to 20 [160,165] blood transfusions or when the serum ferritin level has reached 1,000 ng/mL [94, 160,165]. Growth retardation may result from iron overload or excessive Desferal doses [139,165,166,190]. If chelation is begun before 3 years of age growth must be monitored carefully and the mean daily dose should not exceed 40 mg/kg [105,139,160,165-167,190].

The dosage and the mode of administration may be individually determined and adapted during the course of therapy according to the severity of the patient's iron burden. The lowest effective dosage should be used. To assess the response to chelation therapy, 24-hour urinary iron excretion may initially be monitored daily and the response to increasing doses of Desferal established [10-13]. Once the appropriate dosage has been established, urinary iron excretion rates may be assessed at intervals of a few weeks. Alternatively the mean daily dose may be adjusted according to the ferritin value to keep the therapeutic index less than 0.025 (i.e. mean daily dose (mg/kg) of Desferal divided by the serum ferritin level (micrograms/L) below 0.025 [166,176,190]. The average daily dose of Desferal is usually between 20 and 60 mg/kg [94,165].

In general patients with a serum ferritin level of less than 2,000 ng/mL require about 25 mg/kg/day. Patients with a serum ferritin level between 2,000 and 3,000 ng/mL require about 35 mg/kg/day [94,165]. Patients with higher serum ferritin may require up to 55 mg/kg/day. It is inadvisable regularly to exceed an average daily dose of 50 mg/kg/day except when very intensive chelation is needed in patients who have completed growth [165]. If ferritin values fall below 1,000 ng/mL, the risk of Desferal toxicity increases; it is important to monitor these patients particularly carefully and perhaps to consider lowering the total weekly dose [166,190]. The doses given are the average daily dose. Since most patients take the drug on less than 7 days a week, the actual dose per infusion usually differs from the average daily dose; e.g. if an average daily dose of 40 mg/kg/day is required and the patient wears the pump 5 nights a week, each infusion should contain 56 mg/kg [165].

Regular chelation with Desferal has been shown to improve life expectancy in patients with thalassaemia [138,160,168,169,190].

Slow **subcutaneous infusion** by means of a portable, light-weight infusion pump over a period of 8 to 12 hours is regarded as effective and especially convenient for ambulant patients [48,21,22], but may also be given over a 24-hour period. Desferal should be used with the pump 5 to 7 times a week [48,160,165,166,190]. Desferal is not formulated to support subcutaneous bolus injection.

Intravenous infusion during blood transfusion

The availability of an intravenous line during blood transfusions makes it possible to administer an intravenous infusion with no additional inconvenience to the patient. This is particularly useful for patients who comply poorly with subcutaneous infusions [94,165]. The Desferal solution should not be put directly into the blood bag but may be added to the blood line by means of a "Y" adaptor located near to the venous site of injection. The patient's pump should be used to administer Desferal as usual. Patients and nurses should be warned against accelerating the infusion, as an intravenous bolus of Desferal may lead to acute collapse (see 4.4 Special warnings and precautions for use) [113,165,190].

Continuous intravenous infusion

Implanted intravenous systems can be used when intensive chelation is carried out. Continuous intravenous infusion is indicated in patients who are incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload [95,165,170]. The dose of Desferal depends on the extent of the patient's iron overload. The 24-hour urinary iron excretion should be measured regularly where intensive chelation (i.v.) is required, and the dose adjusted accordingly [94]. Care should be taken when flushing the line to avoid the sudden infusion of residual Desferal which may be present in the dead space of the line, as this may lead to acute collapse (see 4.4 Special warnings and precautions for use) [113,190].

Intramuscular administration

Since the subcutaneous infusions are more effective, intramuscular injections are given only when subcutaneous infusions are not feasible [48,94].

Whichever route of administration is chosen, the individual maintenance dose to be selected will depend on the patient's iron excretion rate.

Concomitant use of vitamin C

Patients with iron overload usually become vitamin C deficient, probably because iron oxidises the vitamin [165]. As an adjuvant to chelation therapy, vitamin C in doses up to 200 mg daily may be given in divided doses, starting after an initial month of regular treatment with Desferal (see 4.4 Special warnings and precautions for use) [94,165]. Vitamin C increases availability of iron for chelation [25-27,165]. In general, 50 mg suffices for children under 10 years of age and 100 mg for older children [94,165]. Larger doses of vitamin C fail to produce any additional increase in excretion of the iron complex [48].

Treatment for acute iron poisoning

Desferal is an adjunct to standard measures generally used in treating acute iron poisoning [61,185,186,189].

Desferal treatment is indicated in any of the following situations [185-187]:

- all symptomatic patients exhibiting more than transient minor symptoms (e.g., more than one episode of emesis or passage of one soft stool),

- patients with evidence of lethargy, significant abdominal pain, hypovolaemia, or acidosis,
- patients with positive abdominal radiograph results demonstrating multiple radiopacities (the great majority of these patients will go on to develop symptomatic iron poisoning),
- any symptomatic patient with a serum iron level greater than 300 to 350 micrograms/dL regardless of the total iron binding capacity (TIBC). It has also been suggested that a conservative approach without Desferal therapy or challenge should be considered when serum iron levels are in the 300 to 500 micrograms/dL range in asymptomatic patients, as well as in those with self-limited, non-bloody emesis or diarrhoea without other symptoms.

The continuous intravenous administration of Desferal is the preferred route and the recommended rate for infusion is 15 mg/kg per hour and should be reduced as soon as the situation permits, usually after 4 to 6 hours so that the total intravenous dose does not exceed a recommended 80 mg/kg in any 24-h period [61,62,97,104,148,185,186,188].

The following suggested criteria are believed to represent appropriate requirements for cessation of Desferal [186,188,189]. Chelation therapy should be continued until the all of the following criteria are satisfied:

- the patient must be free of signs or symptoms of systemic iron poisoning (e.g., no acidosis, no worsening hepatotoxicity),
- ideally, a corrected serum iron level should be normal or low (when iron level falls below 100 micrograms/dL). Given that laboratories cannot measure serum iron concentrations accurately in the presence of Desferal, it is acceptable to discontinue Desferal when all other criteria are met if the measured serum iron concentration is not elevated,
- repeat abdominal radiograph test should be obtained in patients who initially demonstrated multiple radiopacities to ensure they have disappeared before Desferal is discontinued because they serve as a marker for continued iron absorption,
- if the patient initially developed vin-rosé coloured urine with Desferal therapy, it seems reasonable that urine colour should return to normal before halting Desferal (absence of vin-rosé urine is not sufficient by itself to indicate discontinuation of Desferal).

The effectiveness of treatment is dependent on an adequate output of urine in order to ensure that the iron complex ferrioxamine is excreted from the body. If oliguria or anuria develops, peritoneal dialysis, haemodialysis, or haemofiltration may become necessary [61,62].

Treatment for chronic aluminium overload in patients with end-stage renal failure

The iron and aluminium complexes of Desferal are dialysable. In patients with renal failure their elimination will be increased by dialysis [63,65,92].

Patients with evidence of symptoms or organ dysfunction due to aluminium overload should receive Desferal treatment. Even in asymptomatic patients, Desferal treatment should be considered if serum aluminium levels are consistently above 60 ng/mL and are associated with a positive Desferal infusion test (see below), particularly if bone biopsy findings present evidence of aluminium-related bone disease [98,100].

Desferal should be administered with a once-weekly 5 mg/kg dose (see 6.6 Instructions for use and handling). For patients with post-DFO test serum aluminium levels up to 300 ng/mL Desferal should be given as a slow i.v. infusion during the last 60 minutes of a dialysis session [171]. For patients with a post-DFO test serum aluminium value above 300 ng/mL Desferal should be administered by slow i.v. infusion 5 hours prior to the dialysis session [171]. After completing the first 3-month course of Desferal treatment, followed by a 4-week wash-out period, a Desferal infusion test should be performed. If two successive Desferal infusion tests performed at 1-month intervals yield serum aluminium levels less than 50 ng/mL above baseline, further Desferal treatment is not recommended [63,69,71,75,82,84,89,90,92,98-100,171].

In patients on continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD) Desferal should be given once weekly at a 5 mg/kg dose prior to the final exchange of the day [101]. It is recommended that the intraperitoneal route be used in these patients. However, Desferal can also be given i.m., by slow infusion i.v. or s.c. [50,82,83].

Desferal test

This test is based on the principle that in normal subjects Desferal does not raise iron and aluminium excretion above a certain limit.

1. Desferal test for iron overload in patients with normal kidney function

500 mg Desferal should be injected intramuscularly. The urine should then be collected for a period of 6 hours and its iron content determined. An excretion of 1 to 1.5 mg (18 to 27 micromol) during this 6-hour period is suggestive of an iron overload; values of more than 1.5 mg (27 micromol) can be regarded as pathological. The test yields reliable results only in cases where renal function is normal [8,9].

2. Desferal infusion test for aluminium overload in end-stage renal failure patients

A Desferal infusion test is recommended in patients with serum aluminium levels exceeding 60 ng/mL associated with serum ferritin levels above 100 ng/mL.

Just before starting a haemodialysis session, a blood sample is taken to determine the baseline serum aluminium level.

During the last 60 minutes of the haemodialysis session a 5 mg/kg dose (see 6.6 Instructions for use and handling) is given as a slow intravenous infusion [98-100,102].

At the start of the next haemodialysis session (i.e. 44 hours after the aforementioned Desferal infusion) the second blood sample is taken to determine the serum aluminium level once more.

The Desferal test is considered positive if an increase in serum aluminium above the baseline level exceeds 150 ng/mL. A negative test, however, does not absolutely exclude the diagnosis of aluminium overload [24-48,65,71,76,82,98-100].

4.3 Contraindications

Known hypersensitivity to the active substance, except where successful desensitisation makes treatment possible [42-44,103,129,131,172].

4.4 Special warnings and precautions for use

Warnings

Rapid intravenous infusion may lead to hypotension and shock (e.g., flushing, tachycardia, collapse and urticaria) [78,80,94,108,113,153,158,165,190].

High doses of Desferal, especially in patients with low ferritin plasma levels, may lead to disturbances of vision and hearing (see 4.8 Undesirable effects). Patients with renal failure who are receiving maintenance dialysis and have low ferritin levels may be particularly prone to adverse reactions, visual symptoms having been reported after single doses of Desferal [133,137]. The risk of side effects is reduced when low-dose therapy is employed. If visual or auditory disturbances occur, the drug should be discontinued immediately [190]. The changes induced by Desferal are usually reversible if identified early [166,190]. Treatment with Desferal may be resumed later at a reduced dose, with close monitoring of audiovisual function [190].

Approximately half of the metal complex is excreted via the kidneys in iron-overloaded patients with normal renal function [166]. Accordingly, in patients with severe renal failure caution is indicated. The iron and aluminium complexes of desferrioxamine are dialysable; in patients with renal failure their elimination will be increased by dialysis [23,24,92].

Isolated cases of acute renal failure have been reported (see also section 4.8 Undesirable effects) [206].

Patients with low serum ferritin levels on high doses of Desferal, or patients at young age (< 3 years at commencement of treatment) have been associated with growth retardation (see 4.2 Posology and method of administration: “treatment for chronic iron overload”) [105,139,140,165,166,190]. Growth retardation if associated with excessive doses of Desferal must be distinguished from growth retardation from iron overload. Growth retardation from Desferal use is rare if the dose is kept below 40 mg/kg [105]; if growth retardation has been associated with doses above this value, then reduction of the dose may result in return in growth velocity, however, predicted adult height is not attained [105,165].

Acute respiratory distress syndrome has been described following treatment with excessively high i.v. doses of Desferal in patients with acute iron intoxication, and also in thalassaemic patients [143,144,146-148,173]. The recommended daily doses should therefore not be exceeded.

In patients suffering from iron overload it has been reported that Desferal increases susceptibility to infections, e.g. with Yersinia enterocolitica and Yersinia pseudotuberculosis [30-39,113,160,174,190]. If a patient under treatment with Desferal develops fever accompanied by acute enteritis/enterocolitis, diffuse abdominal pain, or pharyngitis, treatment should be temporarily discontinued, bacteriological tests performed, and suitable antibiotic

therapy started at once [190]. After the infection has resolved, treatment with Desferal can be resumed [113,165].

In patients receiving Desferal for aluminium and/or iron overload, rare cases of mucormycosis, some with a fatal outcome, have been reported [77,91,106-112,174,192,201]. If any of the suspected signs or symptoms occur, Desferal should be discontinued, mycological tests carried out and appropriate treatment instituted immediately. Mucormycosis may also occur in patients who are not receiving Desferal, indicating that other factor determinants such as dialysis, diabetes mellitus, disturbance of acid-base balance, haematological malignancies, immunosuppressive drugs, or a compromised immune system may play a role in the development of this infection [107,108,192].

Excretion of the iron complex may cause a reddish-brown discoloration of the urine.

Precautions

Desferal should not be given in doses higher than recommended. The drug should not be given at concentrations higher than 10 % as this increases the risk of local reactions by the subcutaneous route (see 6.6 Instructions for use and handling) [113,165,166,175]. Where intramuscular use is the only option it may be necessary to use higher concentrations to facilitate the injection.

At the recommended concentration of 10 %, the reconstituted solution appears clear, and colourless to slightly yellowish. Only clear solutions should be used. Opaque or cloudy solutions should be discarded. Due care must be taken with the injection technique.

For subcutaneous infusion, the needle should not be inserted too close to the dermis [113].

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with Desferal and high doses of vitamin C (more than 500 mg daily). The cardiac dysfunction was reversible when vitamin C was discontinued. The following precautions should be taken when Desferal and vitamin C are to be used concomitantly [26,28,48,53,94,165]:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Start treatment with vitamin C only after an initial month of regular treatment with Desferal.
- Give vitamin C only if the patient is receiving Desferal regularly, ideally soon after setting up the pump.
- Do not exceed a daily dose of 200 mg of vitamin C, given in divided doses.
- Monitoring of cardiac function is advisable during such combined therapy.

Specialist ophthalmological and audiological testing are recommendable before the start of Desferal treatment and thereafter at regular intervals (every 3 months) particularly if ferritin levels are low [40]. By keeping the ratio of the mean daily dose (mg/kg) of Desferal divided by the serum ferritin (micrograms/L) below 0.025 the risk of audiometric abnormalities may be reduced in thalassaemia patients [176].

Paediatric patients receiving Desferal should be monitored for body weight and longitudinal growth every 3 months (see 4.4 Special warnings and precautions for use) [94,165].

In patients with aluminium-related encephalopathy, high doses of Desferal may exacerbate neurological dysfunction (convulsion), probably owing to an acute increase in circulating aluminium [87] (see section 4.8 Undesirable effects). Desferal may precipitate the onset of dialysis dementia [150]. Pre-treatment with clonazepam has been reported to prevent this neurological deterioration. Also, treatment of aluminium overload may result in decreased serum calcium and aggravation of hyperparathyroidism [114-116].

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with Desferal and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness [41].

In patients with severe chronic iron-storage disease undergoing combined treatment with Desferal and high doses of vitamin C (more than 500 mg daily), impairment of cardiac function has been encountered (see 4.4 Special warnings and precautions for use) [26,28]; this proved reversible when the vitamin C was withdrawn.

Gallium-67-imaging results may be distorted because of the rapid urinary excretion of Desferal-bound gallium 67. Discontinuation of Desferal 48 hours prior to scintigraphy is advisable [118-120].

4.6 Pregnancy and lactation

Pregnancy

Desferrioxamine showed a possible teratogenic potential in rabbits (see 5.3 Preclinical safety data). To date, all patients reported to have received Desferal therapy during pregnancy have born children without any malformations [53,121-125,127-128]. During pregnancy, especially in the first 3 months, it should only be employed if its use is mandatory.

Women of child-bearing potential

In each case the benefits for the mother must be weighed against the risks for the child.

Lactation

It is not known whether desferrioxamine passes into the breast milk.

4.7 Effects on ability to drive and use machines

Patients experiencing dizziness or other central nervous disturbances, or impairment of vision or hearing, should refrain from driving a vehicle or operating machines (see 4.8 Undesirable effects).

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention:*very common* (≥1/10); *common* (≥1/100, <1/10); *uncommon* (≥1/1,000, <1/100); *rare* (≥1/10,000, <1/1,000); *very rare* (<1/10,000) including isolated reports; "*unknown*" (when not possible to reliably estimate the frequency of the adverse reactions reported from post-marketing experience because reports are from a population of uncertain size).

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness [202].

Some of the signs and symptoms reported as adverse effects may also be manifestations of the underlying disease (iron and/or aluminium overload).

Table 1

Infections and infestations		
	Rare:	Mucormycosis (see 4.4 Special warnings and precautions for use) [192].
	Very rare:	Gastroenteritis Yersinia (see 4.4 Special warnings and precautions for use) [192].
Blood and lymphatic system disorders		
	Very rare:	Blood disorder (incl. thrombocytopenia, leukopenia) [154,155,203].
Immune system disorders		
	Very rare:	Anaphylactic shock, anaphylactic reaction, angioneurotic oedema [117,129,131,192].
Nervous system disorders		
	Common:	Headache [175,192].
	Very rare:	Neurological disturbances, dizziness, precipitation or exacerbation of aluminium-related dialysis encephalopathy [108,117,149,150,192], neuropathy peripheral, paraesthesia (see 4.4 Special warnings and precautions for use) [151,192].
	Unknown:	Convulsion (see special remarks below) [204].
Eye disorders		
	Rare:	Loss of vision, scotoma, retinal degeneration, optic neuritis, cataracts, visual acuity decreased, blurred vision, night blindness, visual field defects, chromatopsia (impairment of colour vision), corneal opacities, (see 4.4. Special warnings and precautions for use and Special remarks below) [40,108,113,117,132-137,166,174].
Ear and labyrinth disorders		
	Uncommon:	Deafness neurosensory, tinnitus (see 4.4. Special warnings and precautions for use and Special remarks below)) [40,176].
Vascular disorders		
	Rare:	Hypotension if precautions for administration are not adhered to; see 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use) [78,108,113,116,117,153,158,165,190].
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Asthma [175,192].
	Very rare:	Acute respiratory distress, lung infiltration (see 4.4 Special warnings and precautions for use) [143,144,146-148,153,173].
Gastrointestinal disorders		
	Common:	Nausea.

Uncommon:	Vomiting, abdominal pain [175,192].
Very rare:	Diarrhoea [192].
Skin and subcutaneous tissue disorders	
Common:	Urticaria [192].
Very rare:	Rash generalised [192].
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia [175,192].
Common:	Growth retardation and bone disorder (e.g. metaphyseal dysplasia) in higher doses and young children (see 4.4 Special warnings and precautions for use and Special remarks below) [105,139,141,165,166,177-179,191].
Unknown:	Muscle spasms [205].
Renal and urinary disorders	
Unknown:	Acute renal failure, renal tubular disorder, blood creatinine increased (see 4.4 Special warnings and precautions for use and section 4.9. Overdose) [117,152,153,206].
General disorders and administration site conditions	
Very common:	Injection site reaction including pain, swelling, infiltration, erythema, pruritus, eschar, crust (see Special remarks below) [175,192].
Common:	Pyrexia [175,192].
Uncommon:	Injection site reaction including vesicles, oedema, burning (see Special remarks below) [175,192].

Special remarks

Deafness neurosensory and tinnitus are uncommon if doses are kept within guidelines and if doses are reduced when ferritin levels fall (ratio of the mean daily dose of Desferal divided by the serum ferritin should be below 0.025) [40,176].

The various eye disorders are rare, except if high doses are given (see 4.4. Special warnings and precautions for use) [40,108,113,117,132-137,166,174].

Growth retardation and bone disorder (e.g. metaphyseal dysplasia) are common with doses of above 60 mg/kg [105,141], especially those who begin iron chelation in the first three years of life [139]. With doses of 40 mg/kg or less, the risk is considerably reduced [105,139,141,165,166,177-179,191].

At the injection site pain, swelling, infiltration, erythema, pruritus, and eschar/crust are very common, vesicles, local oedema and burning uncommon reactions [175,192]. The local manifestations may be accompanied by systemic reactions like arthralgia/myalgia (very common), headache (common), urticaria (common), nausea (common), pyrexia (common), vomiting (uncommon), abdominal pain (uncommon) or asthma (uncommon) [175,192].

Convulsion has been mainly reported in dialysed patients with aluminium overload (see 4.4 Special warnings and precautions for use) [204].

Rare cases of increased transaminases have been reported in patients who have been treated with Desferal, however a causality with the drug is not established [207].

4.9 Overdose

Signs and symptoms

Inadvertent administration of an overdose or inadvertent intravenous bolus administration/rapid intravenous infusion may be associated with hypotension, tachycardia and gastrointestinal disturbances; acute but transient loss of vision, aphasia, agitation, headache, nausea, bradycardia, as well as acute renal failure (see section 4.8 Undesirable effects) have been reported [78,80,113,153,157,158,165,190].

Treatment

There is no specific antidote. Desferal should be discontinued and appropriate symptomatic measures undertaken.

Desferal is dialysable.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Chelating agent (ATC code: V03ACO1).

Mechanism of action

Desferrioxamine (DFO) forms complexes predominantly with ferric iron and with trivalent aluminium ions: the complex formation constants are 10^{31} and 10^{25}, respectively [45,46]. The affinity of DFO for divalent ions such as Fe^{2+}, Cu^{2+}, Zn^{2+}, Ca^{2+} is substantially lower (complex formation constants 10^{14} or below). Chelation occurs at a 1:1 molar basis, so that 1 g DFO can theoretically bind 85 mg ferric iron or 41 mg Al^{3+} [47,48].

Owing to its chelating properties, DFO is capable of taking up free iron, either in plasma or in cells thereby forming the complex ferrioxamine (FO) [47,180]. Urinary iron excretion of FO is predominantly a reflection of iron derived from plasma turnover whereas faecal iron reflects mainly intrahepatic iron chelation [166,181,182]. Iron may be chelated from ferritin and haemosiderin [47] but is relatively slow at clinically relevant concentrations of DFO. DFO, however, does not remove iron from transferrin or from haemoglobin or from other haemin-containing substances [47].

DFO can also mobilise and chelate aluminium, forming an aluminoxamine (AlO) complex [50].

Pharmacodynamic effects

Since both complexes, FO and AlO, are completely excreted, DFO promotes the excretion of iron and aluminium in the urine and faeces and thus reduces pathological iron or aluminium deposits in the organs [85,86].

5.2 Pharmacokinetic properties

Absorption

DFO is rapidly absorbed after intramuscular bolus injection or slow subcutaneous infusion [1,2], but only poorly absorbed from the gastrointestinal tract in the presence of intact mucosa [93,126,130]. The absolute bioavailability is less than 2 % after oral administration of 1 g DFO [130].

During peritoneal dialysis DFO is absorbed if administered in the dialysis fluid [50].

Distribution

In healthy volunteers peak plasma concentrations of 15.5 micromol/L (8.7 micrograms/mL) were measured 30 minutes after an intramuscular injection of 10 mg/kg DFO [49]. One hour after injection the peak concentration of FO was 3.7 micromol/L (2.3 micrograms/mL). After intravenous infusion of 2 g (about 29 mg/kg) of DFO to healthy volunteers over 2 hours mean steady state concentrations of DFO of 30.5 micromol/L were reached; distribution of DFO is very rapid with a mean distribution half-life of 0.4 hours [183]. Less than 10 % of DFO is bound to serum proteins *in vitro* [3].

Biotransformation

Four metabolites of DFO were isolated and identified from urine of patients with iron overload. The following biotransformation reactions were found to occur with DFO: transamination and oxidation yielding an acid metabolite, beta-oxidation also yielding an acid metabolite, decarboxylation and N-hydroxylation yielding neutral metabolites [142,145].

Elimination

Both DFO and FO have a biphasic elimination after intramuscular injection in healthy volunteers [49]; for DFO the apparent distribution half-life is 1 hour, and for FO 2.4 hours. The apparent terminal half-life is 6 hours for both. Within six hours of injection, 22 % of the dose appears in the urine as DFO and 1 % as FO.

Characteristics in patients

In **patients with haemochromatosis** peak plasma levels of 7.0 micromol/L (3.9 micrograms/mL) were measured for DFO, and 15.7 micromol/L (9.6 micrograms/mL) for FO, 1 hour after an intramuscular injection of 10 mg/kg DFO. These patients eliminated DFO and FO with half-lives of 5.6 and 4.6 hours, respectively. Six hours after the injection 17 % of the dose was excreted in the urine as DFO and 12 % as FO [49].

In **patients with thalassaemia** continuous intravenous infusion of 50 mg/kg/24 h of DFO resulted in plasma steady state levels of DFO of 7.4 micromol/L (4.1 micrograms/mL) [181]. Elimination of DFO from plasma was biphasic with a mean distribution half-life of 0.28 hours and an apparent terminal half-life of 3.0 hours [181]. The total plasma clearance was 0.5 L/h/kg and the volume of distribution at steady state was estimated at 1.35 L/kg [181].

Exposure to the main iron binding metabolite was around 54 % of that of DFO in terms of AUC [181]. The apparent monoexponential elimination half-life of the metabolite was 1.3 hours [181].

In **patients dialysed for renal failure** who received 40 mg/kg DFO infused i.v. within 1 hour, the plasma concentration at the end of the infusion was 152 micromol/L (85.2 micrograms/mL) when the infusion was given between dialysis sessions [92]. Plasma concentrations of DFO were between 13 % and 27 % lower when the infusion was administered during dialysis. Concentrations of FO were in all cases approx. 7.0 micromol/L (4.3 micrograms/mL); and for AlO 2-3 micromol/L (1.2-1.8 micrograms/mL). After the infusion was discontinued, the plasma concentration of DFO decreased rapidly with a half-life of 20 minutes [51]. A smaller fraction of the dose was eliminated with a longer half-life of 14 hours. The plasma concentrations of AlO continued to increase for up to 48 hours after the infusion and reached values of approx. 7 micromol/L (4 micrograms/mL) [92]. Following dialysis the plasma concentration of AlO dropped to 2.2 micromol/L (1.3 micrograms/mL).

5.3 Preclinical safety data

The subcutaneous administration of high doses of DFO to rats, dogs and cats for several weeks caused eye-lens opacity with cataract formation [193,194].

DFO did not show evidence for genotoxic/mutagenic effects in *in vitro* assays (Ames test) and *in vivo* assay (micronucleus test in rats) [193,195-199]. Long-term carcinogenicity studies have not been performed.

DFO was not teratogenic in rats and mice [193,200]. In rabbit foetuses, which were exposed in utero to maternally toxic doses, some malformations of the axial skeleton were found [193]. Though the results of this study are considered of a preliminary character, DFO-induced teratogenicity in rabbits cannot be excluded under the experimental conditions employed.

6 Pharmaceutical particulars

6.1 List of excipients

Not applicable.

Information might differ in some countries.

6.2 Incompatibilities

- Heparin injectable solution.
- Physiological saline (0.9 %) should not be used as a solvent for the dry substance; but, after reconstitution of the Desferal solution with water for injection, it can be employed for further dilution.

6.3 Shelf life

4 years.

Information might differ in some countries.

6.4 Special precautions for storage

Store the vials containing the dry active substance below 25 °C.

One vial is for single use only. The product should be used immediately after reconstitution (commencement of treatment within 3 hours). When reconstitution is carried out under validated aseptic conditions the product may be stored for a maximum period of 24 hours at room temperature before administration.

Information might differ in some countries.

Desferal must be kept out of the reach and sight of children.

6.5 Nature and content of container

Colourless glass vials in the sizes 7.5 mL and 50 mL, with rubber closures.

6.6 Instructions for use and handling, and disposal (if appropriate)

When administered parenterally, the drug should be used as a 10 % solution in water for injection [94] except for i.m. injection where a higher concentration may be necessary. 5 mL water for injection is injected into the vial containing 500 mg Desferal powder, and the vial is shaken well. Only clear and colourless to slightly yellowish solutions should be used. The 10 % Desferal solution can be further diluted with routinely employed infusion solutions (NaCl 0.9 %, glucose 5 %, Ringer's solution, Ringer-Lactate solution, peritoneal dialysis solutions such as Dianeal 137 Glucose 2.27 %, Dianeal PD4 Glucose 2.27 %, and CAPD/DPCA 2 Glucose 1.5 %).

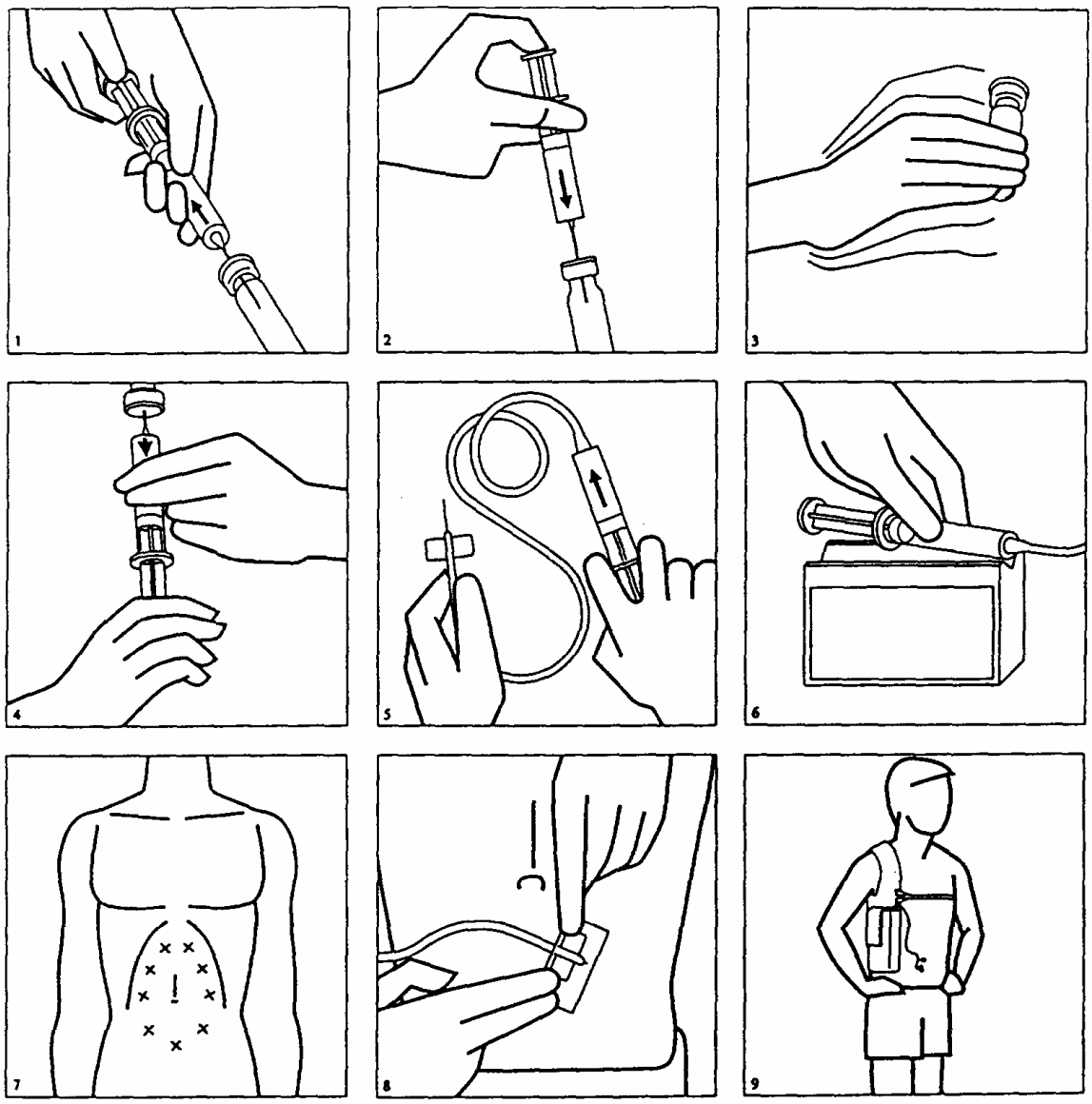
For the Desferal infusion test and the treatment of chronic aluminium overload, the 5 mL Desferal solution in the vial is an adequate dose (5 mg/kg) for a patient with 100 kg body weight. According to the actual body weight of the patient, the appropriate amount of Desferal solution is withdrawn from the vial and added to 150 mL 0.9 % saline (NaCl solution).

Dissolved Desferal can also be added to the dialysis fluid and given intraperitoneally to patients on CAPD or CCPD [88].

The use of Desferal in chronic iron overload by means of a portable infusion pump is described in the patient information as follows (for illustrations see below):

1. Draw the water for injection into a syringe.
2. After cleaning the rubber stopper of the Desferal vial with alcohol, inject the content of the syringe into the vial.
3. Shake the vial well to dissolve the drug.
4. Draw the dissolved drug into the syringe.
5. Attach the extension tube to the syringe, connect the extension tube to the butterfly-type needle, and then fill the empty space in the tube with the solution in the syringe.

6. Place the syringe into the infusion pump.
7. For infusion you may insert the butterfly-type needle under the skin of the abdomen, the arm, upper leg, or the thigh. It is important to clean the skin very thoroughly with alcohol before you insert the needle firmly up to the wings into a fold of the skin, formed by your free hand. The tip of the needle should move freely when the needle is waggled. If it doesn't move freely, the tip of the needle may be too close to the skin. Try again at a new site after cleaning it with alcohol.
8. Then fix the needle and tape it down.
9. Patients usually wear the pump on the body using a belt or shoulder holster. Many patients regard overnight use as the most convenient.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