Ferriprox®
deferiprone

FIRST PRIORITY CARDIAC IRON REDUCTION

Ferriprox (deferiprone) increases survival and reduces cardiac iron compared with deferoxamine in thalassaemia major (TM)[1-6]

Prescribing information is available on pages 25-27

1. Ferriprox Summary of Product Characteristics.
2. Pennell D, et al. Blood. 2006;107(9):3738-3744.
3. Maggio et al, Blood Cells Mol Dis. 2009;42(3):247-51.
4. Piga A, et al. Haematologica. 2003;88(5):489-496.
5. Ceci A et al, Haematologica 2006; 91:1420-1421.
6. Ladis V, Eur J Haematol. 2010 Oct;85(4):335-44.

Chiesi
global rare diseases

Ferriprox®
deferiprone

FERRIPROX LICENSED AS MONOTHERAPY OR COMBINATION THERAPY[1]

Indication

Combination therapy licence provides flexible treatment options in thalassaemia major (TM)

MONOTHERAPY

Ferriprox monotherapy is indicated for the treatment of iron overload in patients with TM when current chelation therapy is contraindicated or inadequate[1]

COMBINATION

Ferriprox in combination with another chelator is indicated in patients with TM when monotherapy with any iron chelator is ineffective or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction[1]

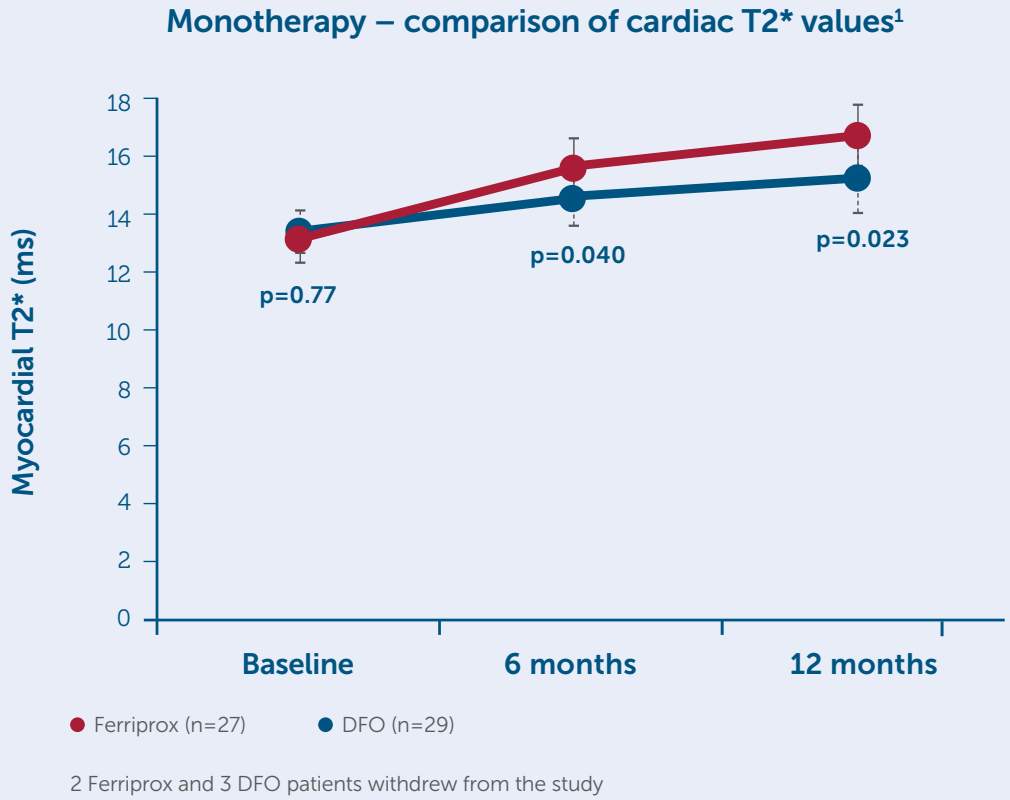
1. Ferriprox Summary of Product Characteristics.

FERRIPROX REDUCES CARDIAC IRON LOAD IN TM: MONOTHERAPY[1]

Cardiac iron

Decrease in cardiac iron load with monotherapy

A randomised, prospective study over 12 months (n=61)[1]



2 Ferriprox and 3 DFO patients withdrew from the study

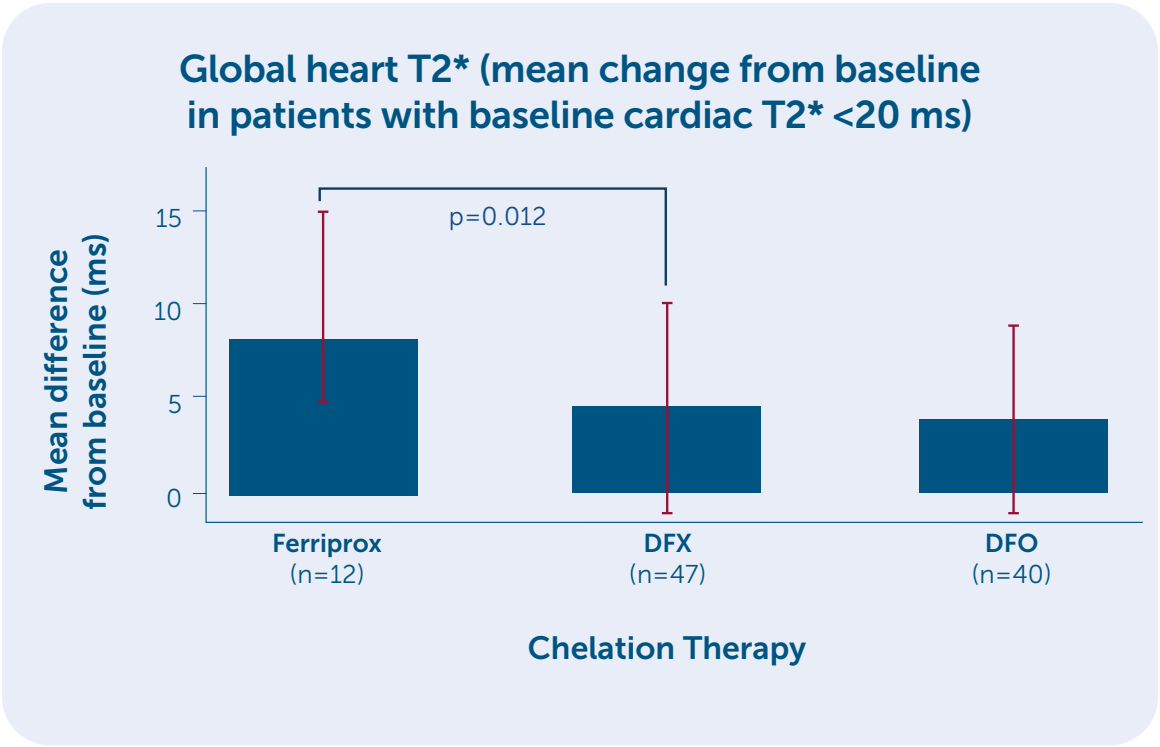
Adapted from Pennell et al., 2006[1]

Ferriprox monotherapy reduced cardiac iron burden significantly more than DFO as assessed by T2*: 27% vs. 13% (p=0.023)[1]

1. Pennell D, et al. Blood. 2006;107(9):3738-3744.

DFO = deferoxamine.

FERRIPROX REDUCES MRI CARDIAC IRON IN TM: MONOTHERAPY[1]



Adapted from Pepe et al., 2018[1]

Mean administered dosages:
Ferriprox: 73.9 ± 12.9 mg/kg (frequency = 6.9 ± 0.5 days/week); DFX: 26.0 ± 6.5 mg/kg (frequency = 7 days/week);
DFO: 40.6 ± 6.9 mg/kg (frequency = 5.6 ± 0.8 days/week)

- Prospective multicentre study published in 539 TM patients receiving chelator monotherapy (both baseline and follow-up data available were available for 444 patients)[1]
- Mean time between MRI scans was approximately 18 months (with no difference between groups)[1]
- For patients with baseline cardiac T2* <20 ms (n=99):[1]
  - Global heart T2* improvement and changes in global heart T2* per month were significantly higher for Ferriprox vs DFX (p=0.032 for percentage changes per month)
  - Reduction in MRI cardiac iron concentration was significantly higher with Ferriprox than DFX (p=0.044 for mean difference from baseline)
  - The difference between Ferriprox and DFX remained significant when adjusting for serum ferritin levels (p=0.047)
- The percentage of patients who maintained a normal global heart T2* was comparable between Ferriprox and DFX (97.7% vs 98.9%; p=0.381)

1. Pepe A, et al. Br J Haematol 2018;183(5):783-95.

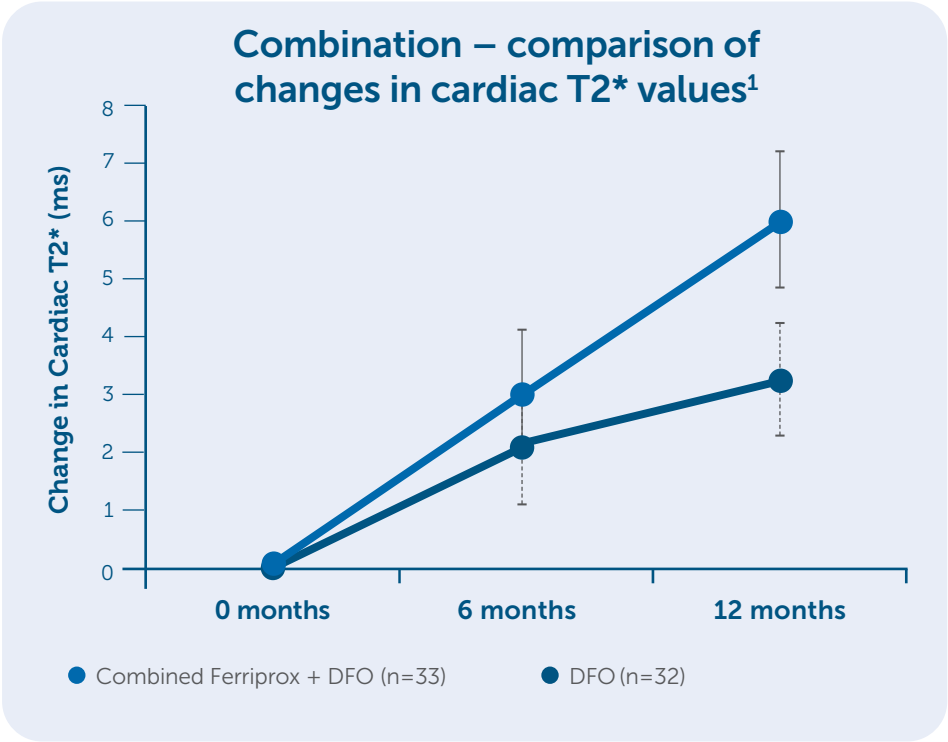
DFO = deferoxamine.
DFX = deferasirox.
MRI = magnetic resonance imaging.
TM = thalassaemia major.

FERRIPROX REDUCES CARDIAC IRON IN TM: COMBINATION THERAPY[1]

Cardiac iron

Decrease in cardiac iron load with combination therapy

A randomised, prospective study (n=65) over 12 months of treatment (double-blind comparison DFO/Ferriprox n=[33]; DFO alone n=[32])[2]



Myocardial T2* showed a significantly larger improvement from baseline in the combination therapy group than in the DFO group (ratio of change in geometric means 1.50 versus 1.24; P=0.02)[1]

Adapted from Tanner et al., 2007[1]

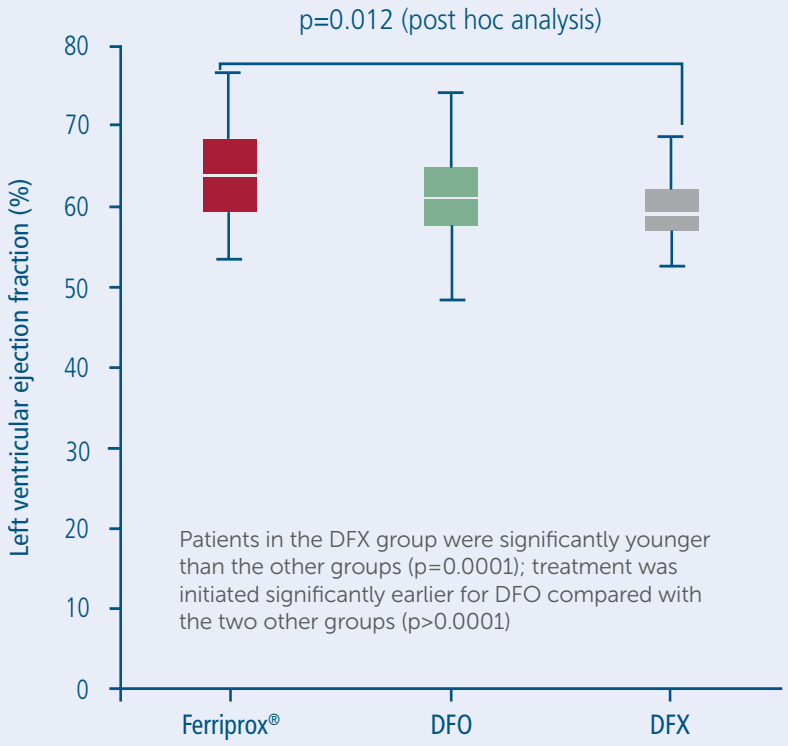
The mean dose of DFO in all randomised patients (DFO and combined groups) before trial entry was 36.4±11.1 mg/kg per day for 5.5 days/week (equivalent to 40.5 mg/kg for 5 days/week). This is in accord with the 40 to 50 mg/kg per day for 5 days/week from clinical recommendations. During the trial, the dose prescribed for DFO in the DFO group was equivalent to 43.4 mg/kg per day for 5 days/week (2.5±9.2 mg/kg per day; p=0.1 vs. pretrial maintenance dose for the DFO group only). In comparison, the dose prescribed in the combined group during the trial was significantly lower at 34.9 mg/kg per day for 5 days (p=0.02 vs. DFO group). At baseline, no patient was taking deferiprone. During the trial, the dose prescribed for deferiprone was 75 mg/kg per day for all patients[1]

1. Tanner MA, et al. Circulation. 2007;115(14):1876-84.
2. Ferriprox Summary of Product Characteristics.

DFO = deferoxamine.
TM = thalassaemia major.

FERRIPROX IMPROVES LVEF IN TM: MONOTHERAPY[1,2]

Monotherapy - comparison of effect on ejection fraction[1,2]



Each box shows the median, quartiles and extreme values within the category

Adapted from Pepe et al., 2011[1]

In other studies, patients taking Ferriprox maintained or improved LVEF and RVEF compared to patients taking DFO or DFX[2,3]

Ferriprox is not indicated for improvement of cardiac function outside of TM[4]

A retrospective analysis (Ferriprox, n=42; DFO, n=89; DFX, n=24;)[1]

- Patients on Ferriprox showed less myocardial iron burden compared with DFO or DFX. The authors note the improved efficacy in removing or preventing cardiac iron may result in a concordant positive effect on heart function
- Ferriprox showed significantly higher LVEF vs. the DFO and DFX groups (p=0.01)[1]
- In a long-term study (n=168 TM patients followed for ≥5 years), Ferriprox monotherapy showed significantly better LVEF vs. DFO monotherapy (p=0.002)[2]

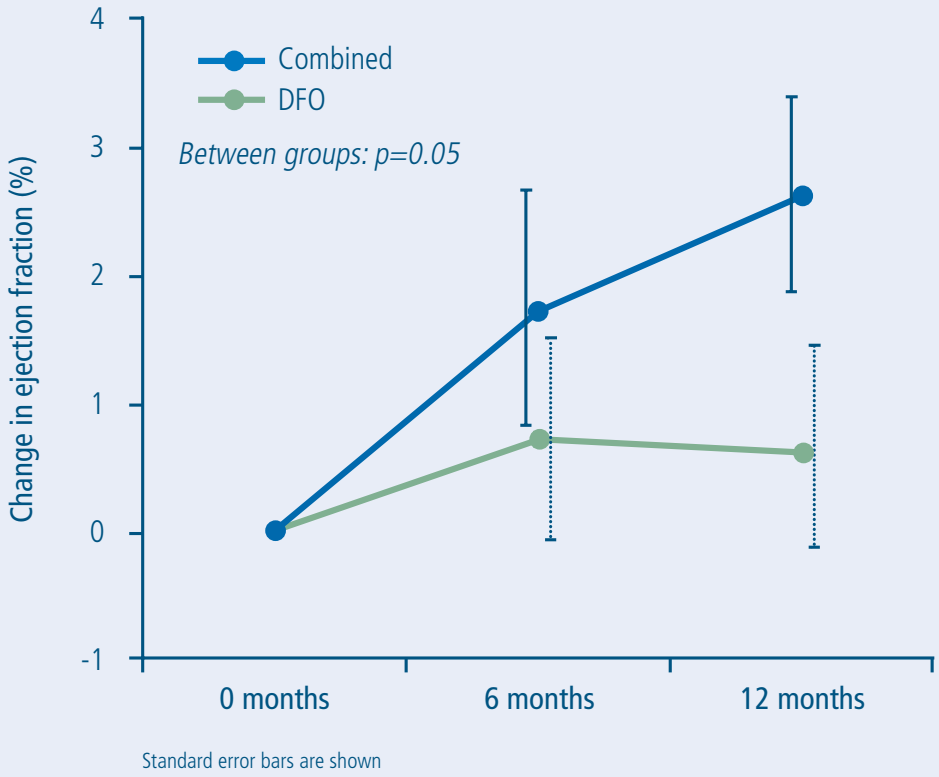
1. Pepe A, et al. Haematologica. 2011;96(1):41-7.
2. Filosa A, et al. Blood Cells Mol Dis. 2013;51(2):85-8.
3. Smith GC, et al. Cardiovasc Magn Reson. 2011;13:34.
4. Ferriprox Summary of Product Characteristics.

DFO= deferoxamine.
DFX = deferasirox.
LVEF = left ventricular ejection fraction.
TM = thalassaemia major.
RVEF = right ventricular ejection fraction.

FERRIPROX IMPROVES CARDIAC FUNCTION IN TM: COMBINATION THERAPY[1]

Cardiac function

A randomised, prospective study (n=65) over 12 months of treatment (double-blind comparison DFO/Ferriprox [n=33]; DFO alone [n=32])[1,2]



Adapted from Tanner et al., 2007[1]

- Increase from 65.8 ± 6.2% at baseline to 68.4 ± 4.7% at 12 months for Ferriprox/DFO combination compared with 64.7 ± 6.5% to 65.3 ± 6.0% for monotherapy[1]
- Improvements in LVEF are most obvious in patients with the highest cardiac iron burden (T2*<10 ms)[1]

Ferriprox in combination with DFO demonstrates superior reduction in myocardial iron over DFO alone[1]

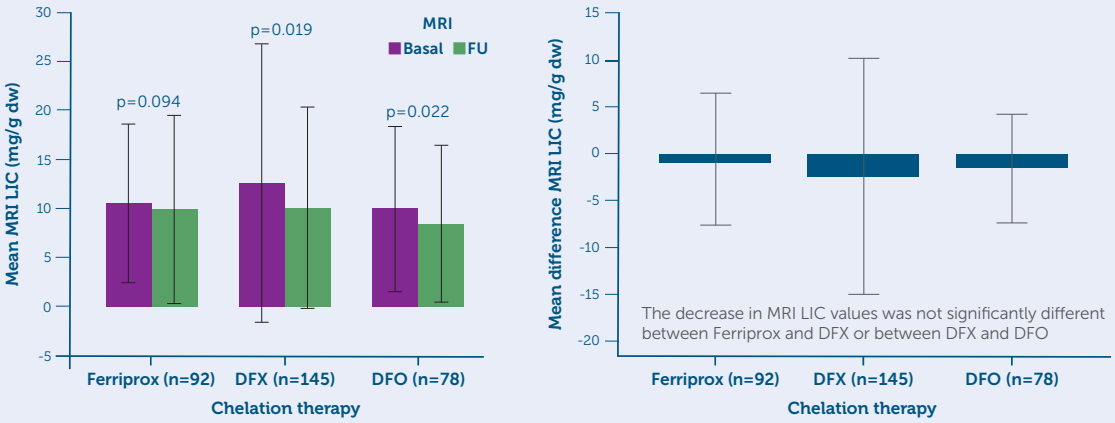
Patients treated with Ferriprox in combination with DFO showed significantly increased LVEF over 12 months of treatment, compared with patients taking DFO alone[1]

1. Tanner MA, et al. Circulation. 2007;115(14):1876-84.
2. Ferriprox Summary of Product Characteristics.

DFO = deferoxamine.
LVEF = left ventricular ejection fraction.
TM = thalassaemia major.

FERRIPROX ACHIEVES SIMILAR REDUCTION IN LIVER IRON AS DFX AND DFO: MONOTHERAPY[1]

Intra- and inter-treatment comparisons in patients with a baseline MRI LIC >3mg/g dw



Adapted from Pepe et al., 2018[1]

Mean administered dosages were Ferriprox: 76.7 ± 11.3 mg/kg (frequency = 6.9 ± 0.6 days/week); DFX: 27.6 ± 6.2 mg/kg (frequency = 7 days/week); DFO: 42.4 ± 6.2 mg/kg (frequency = 5.7 ± 0.8 days/week)

- Prospective multicentre study published in 539 TM patients receiving chelator monotherapy (both baseline and follow-up data available were available for 444 patients). Mean time between MRI scans was approximately 18 months[1]
- For patients with a baseline MRI LIC >3mg/g dw:
  - Changes in MRI liver iron concentration were comparable between groups
  - All patients on Ferriprox and DFX who lowered their liver iron concentration by >50% improved their cardiac iron
- Mean MRI LIC at baseline was numerically higher for DFX vs Ferriprox (12.6 vs 10.5 mg/g dw)

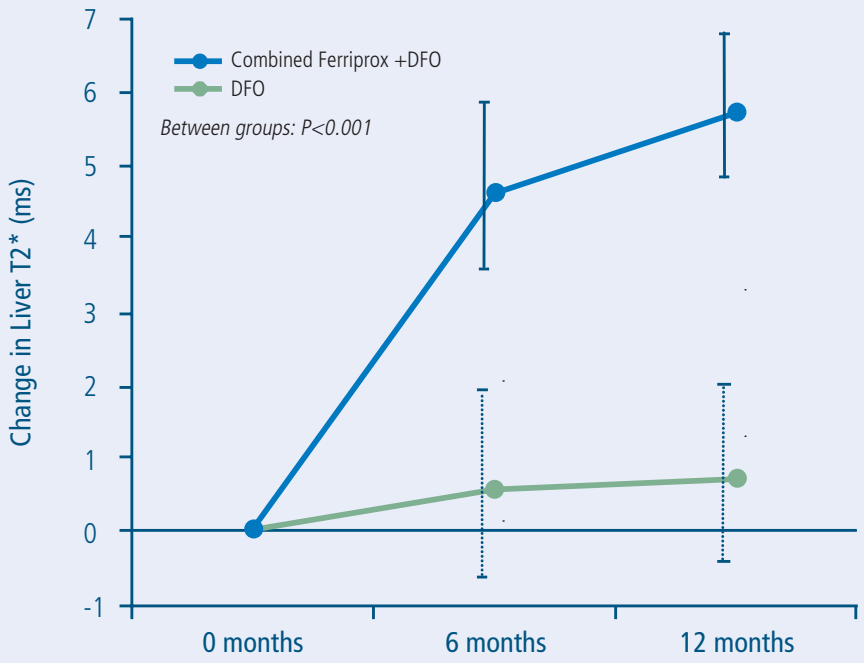
1. Pepe A, et al. Br J Haematol 2018;183(5):783-95.

DFO= deferoxamine.
DFX = deferasirox.
LIC = liver iron concentration.
MRI = magnetic resonance imaging.

FERRIPROX REDUCES LIVER IRON IN TM: COMBINATION THERAPY[1]

Liver iron

Combination - comparison of liver T2* values[1]



Liver T2* showed a significantly larger improvement from baseline in the combined (Ferriprox and DFO) group than in the DFO monotherapy group[1]

Adapted from Tanner et al., 2007[1]

Mean change in overall LIC[2]

Regime	Time (years)	Overall		
		n	△ LIC	P-value
DFO	2.0	36	+1.34	0.095
Ferriprox	1.9	14	-6.2	0.068
Combination	1.8	99	-4.19	<0.001
DFX	1.3	53	-2.80	0.0005

Retrospective study comparing four different chelation regimens (n=232 who have had at least two MRIs of the heart and liver minimum 12 months apart)[2]

- Ferriprox/DFO combination resulted in the most rapid decline both in cardiac and liver iron load[2]

1. Tanner MA, et al. Circulation. 2007;115(14):1876-84.
2. Berdoukas V, et al. J Cardiovasc Mag Res. 2009;11:20.

DFO = deferoxamine.
LIC = liver iron concentration.
MRI = magnetic resonance imaging.

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FERRIPROX ACHIEVES SIMILAR REDUCTION IN SERUM FERRITIN AS DFO: MONOTHERAPY[1]

Monotherapy - total body iron chelation measured by serum ferritin levels

Comparison with DFO[1]

- Clinical studies compared the efficacy of Ferriprox with that of DFO in controlling serum ferritin in transfusion-dependent TM patients
- Ferriprox and DFO were equivalent in promoting a net stabilization or reduction of body iron load, despite the continuous transfusional iron administration in those patients
- There was no difference in the proportion of patients with a negative trend in serum ferritin between the two treatment groups by regression analysis ($p>0.05$)

1. Ferriprox Summary of Product Characteristics.

DFO = deferoxamine.

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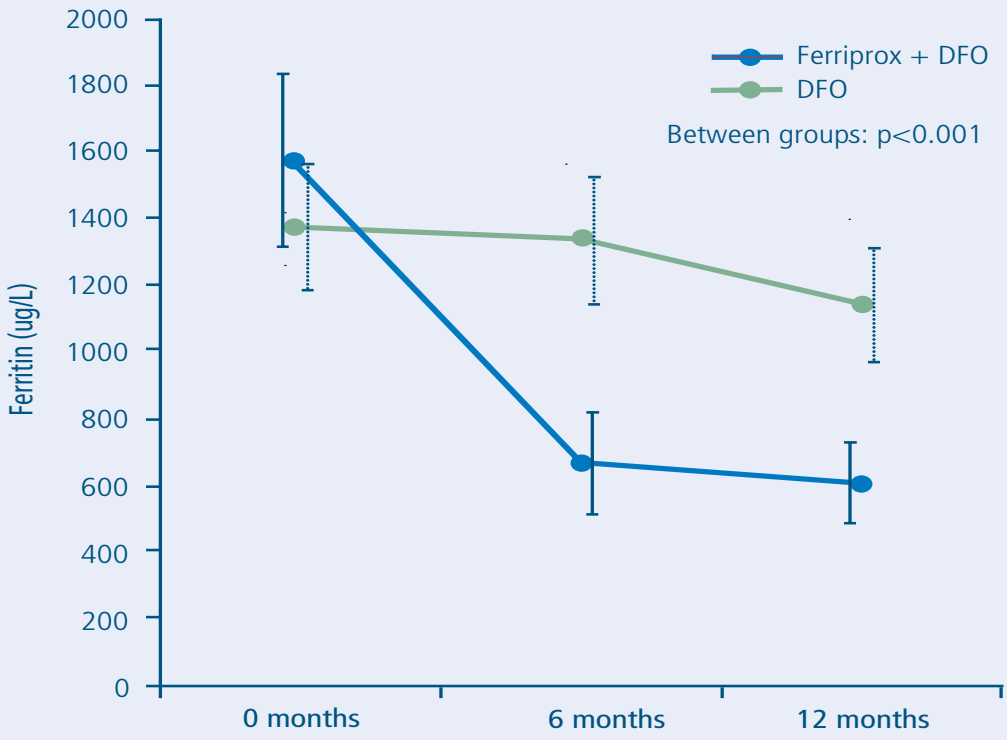
FERRIPROX REDUCES TOTAL BODY IRON IN TM: COMBINATION THERAPY[1]

Total body iron

Combination - comparison of serum ferritin reduction[1]



Adapted from Tanner et al., 2007[1]

- Significant reduction in serum ferritin in Ferriprox/DFO combined group (n=32), from 1574 µg/L at baseline to 598 µg/L at 12 months p<0.0011
- Between-group difference significantly in favour of Ferriprox combined with DFO versus DFO monotherapy (-40%; 95% CI, -48% to -28%; p<0.001)[1]

Ferriprox in combination with DFO reduces total body iron[2]

1. Tanner MA, et al. Circulation. 2007;115(14):1876-84.
2. Jamuar SS, Lai AHM. *Ther Adv Hematol.* 2012;3(5):299-307.

DFO = deferoxamine.

FERRIPROX HAS A MANAGEABLE TOLERABILITY PROFILE[1]

Tolerability

The Ferriprox tolerability profile has been established in over 70 studies worldwide

Agranulocytosis/severe neutropenia (ANC <0.5 x 10^9/L)

In clinical trials of Ferriprox-treated patients:[1]

- **Agranulocytosis/severe neutropenia occurred in 1.1% of patients**
  - Agranulocytosis is not Ferriprox dose dependent, and is most common in the first year of therapy
    - 63% of episodes occurred within the first six months of treatment 74% within the first year, and 26% after one year of therapy
  - A fatal outcome was observed in 8.3% of the reported episodes of agranulocytosis from clinical trials and post-marketing experience

Neutropenia (ANC <1.5 x 10^9/L)[1]

- Neutropenia occurred in 4.9% of patients. This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism
- Neutropenia may foreshadow agranulocytosis

1. Ferriprox Summary of Product Characteristics

.ANC = absolute neutrophil count.

MOST COMMON ADVERSE EFFECTS WITH FERRIPROX[1]

Tolerability

Most common adverse events

Adverse reaction frequencies: Very common (≥1/10), Common (≥1/100 to <1/10)[1]		
SYSTEM ORGAN CLASS	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis
Metabolism and nutrition disorders		Increased appetite
Nervous system disorders		Headache
Gastrointestinal disorders	Nausea Abdominal pain Vomiting	Diarrhoea
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders	Chromaturia	
General disorders and administration site conditions		Fatigue
Investigations		Increased liver enzymes

1. Ferriprox Summary of Product Characteristics

MONITORING PATIENTS ON FERRIPROX[1]

Absolute neutrophil count (ANC)[1]

Once weekly monitoring during the first year of therapy[1]

The patient's ANC should be monitored every week during the first year of therapy.

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on deferiprone, therapy should be immediately interrupted, and an ANC obtained without delay. The neutrophil count should be then monitored more frequently.

Less frequent monitoring after 1 year of treatment[1]

For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of Ferriprox therapy.

The change from weekly ANC monitoring to at the time of transfusion visits after 12 months of Ferriprox therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy.

Patients should be aware to contact their physician if they experience any symptoms indicative of infection (such as fever, sore throat and flu-like symptoms). Immediately interrupt deferiprone if the patient experiences infection

1. Ferriprox Summary of Product Characteristics.

ANC = absolute neutrophil count.
ALT = alanine aminotransferase.

MONITORING PATIENTS ON FERRIPROX[1]

Monitoring

Serum liver enzymes[1]

Regular monitoring

- Increased ALT levels were observed in clinical trials. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone.

  There are no data available on the use of deferiprone in patients with end stage renal disease or severe hepatic impairment. Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be monitored in these patient populations during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone th erapy should be considered. In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Neurological disorders[1]

- Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but have also been observed with standard doses of deferiprone.

  Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. Deferiprone use should be discontinued if neurological disorders are observed.

1. Ferriprox Summary of Product Characteristics.

ANC = absolute neutrophil count.

SUGGESTED MANAGEMENT OF CASES OF NEUTROPENIA[1]

Monitoring

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher if the baseline ANC is less than 1.5x10^9/l.

For neutropenia events (ANC < 1.5x10^9/l and > 0.5x10^9/l):

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic regimen instituted.

For agranulocytosis (ANC < 0.5x10^9/l):

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

1. Ferriprox Summary of Product Characteristics.

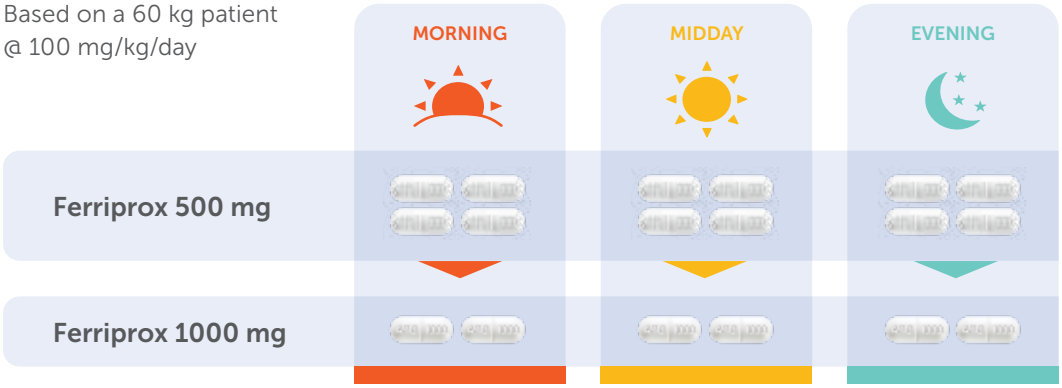
ANC = absolute neutrophil count.

FERRIPROX OFFERS FLEXIBLE DOSING[1]

Dosing

Example:

Based on a 60 kg patient
@ 100 mg/kg/day



FERRIPROX 1000 MG TABLETS REDUCE PILL BURDEN

Initiate dose at:

75 mg/kg/day

Increase to a maximum of:

100 mg/kg/day

Use in patients with renal or hepatic impairment

- In clinical studies, no significant effect of renal or hepatic impairment was seen on systemic exposure to Ferriprox[1]
- No adjustment of the Ferriprox dosage regimen is required in patients with impaired renal function (mild to severe) or in mild to moderately impaired hepatic function. The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment or end stage renal failure has not been established[1]

1. Ferriprox Summary of Product Characteristics.

FERRIPROX OFFERS A CHOICE OF FORMULATIONS

Ferriprox is available as 500 mg and 1000 mg tablets and 100 mg/mL oral solution

Ferriprox®
deferiprone

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WHAT ARE THE KEY TARGET ORGANS FOR IRON ACCUMULATION?

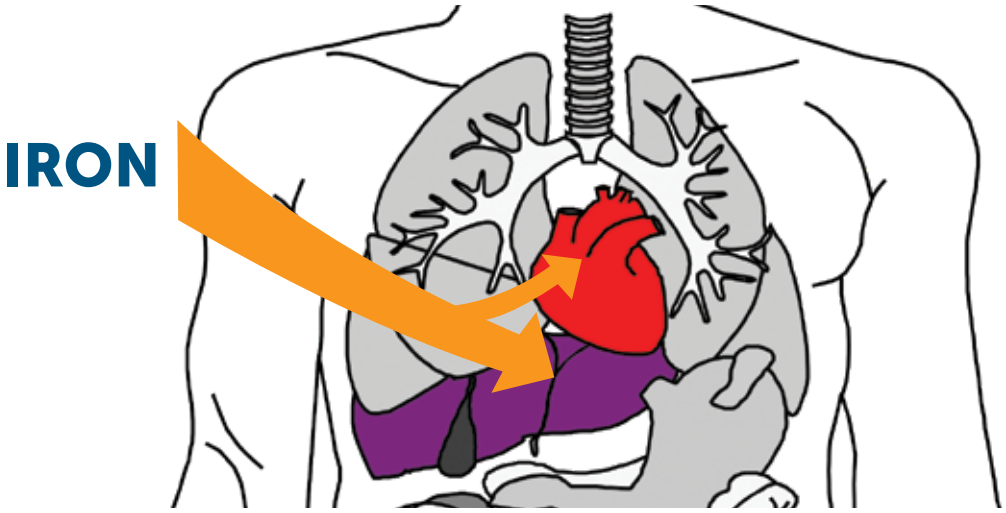
Supporting information

Iron chelation is important for patients with thalassaemia who receive repeated blood transfusions

Repeated blood transfusions cause excess labile iron to circulate in the plasma[1]

The liver is the main site for iron storage. Excess iron can be removed with iron chelation[1,2]

The iron that goes into the heart is more difficult to remove. Different chelators have different capabilities in removing iron from the heart[1,2]



"Serum ferritin and liver iron concentration (LIC) are not adequate surrogates for cardiac iron measurement"[3]

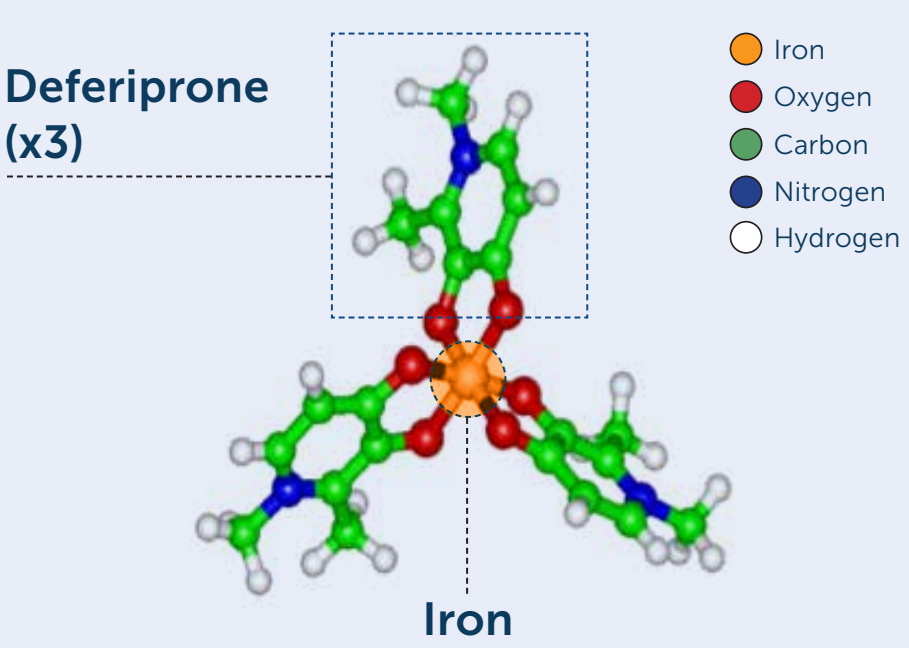
1. Thalassaemia International Federation. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd edition. Nicosia (CY): Thalassaemia International Federation; 2014. Editors Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V.
2. Noetzil LJ, et al. Blood 2008;112:2973-2978.
3. Pennell DJ, et al. Circulation. 2013;128:281-308.

FERRIPROX MECHANISM OF ACTION

Supporting information

Ferriprox is a bidentate ligand that binds to iron in a 3:1 molecular ratio[1]

Ferriprox has been proven effective in removing excess cardiac iron. This may be related to its high ability to enter myocardial cells due to its low molecular weight, neutral charge, and lipophilicity[2]



Chelator molecular weights[3]		
Ferriprox	**Deferasirox (DFX)**	**Deferoxamine (DFO)**
139 Da	373 Da	560 Da

1. Ferriprox Summary of Product Characteristics.
2. Jamuar, et al. Ther Adv Hematol. 2012;3(5)299-307.
3. Thalassaemia International Federation. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd edition. Nicosia (CY): Thalassaemia International Federation; 2014. Editors Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V.

Da = daltons.

FERRIPROX DOSE TABLE (500 MG TABLETS)

Supporting information

An oral treatment with flexible dosing[1]

Ferriprox is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg. Dose per kilogram body weight should be calculated to the nearest 2.5 ml for the oral solution

To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed

Dose table for Ferriprox 500 mg film-coated tablets

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/ day)	Number of tablets (three times/day)
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

Ferriprox is available as: 500 mg and 1000 mg tablets and an oral solution 100 mg/ml[1]

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions; chronic administration of more than 2.5 times the maximum recommended dose has been associated with neurological disorders

It is recommended that serum ferritin concentrations or other indicators of body iron overload be monitored every 2-3 months after starting Ferriprox. Dose adjustments should be tailored to the individual patient's response and therapeutic goals. Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l

1. Ferriprox Summary of Product Characteristics.

FERRIPROX DOSE TABLE (1000 MG TABLETS)

Supporting information

An oral treatment with flexible dosing[1]

Ferriprox is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg. Dose per kilogram body weight should be calculated to the nearest 2.5 ml for the oral solution

To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed

Dose table for Ferriprox 1000 mg film-coated tablets

Body weight (kg)	Total daily dose (mg)	Number of 1000 mg tablets*		
		Morning	Midday	Evening
20	1500	0.5	0.5	0.5
30	2250	1.0	0.5	1.0
40	3000	1.0	1.0	1.0
50	3750	1.5	1.0	1.5
60	4500	1.5	1.5	1.5
70	5250	2.0	1.5	2.0
80	6000	2.0	2.0	2.0
90	6750	2.5	2.0	2.5

*number of tablets rounded to nearest half tablet

Ferriprox is available as: 500 mg and 1000 mg tablets and an oral solution 100 mg/ml[1]

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions; chronic administration of more than 2.5 times the maximum recommended dose has been associated with neurological disorders

It is recommended that serum ferritin concentrations or other indicators of body iron overload be monitored every 2-3 months after starting Ferriprox. Dose adjustments should be tailored to the individual patient's response and therapeutic goals. Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l

1. Ferriprox Summary of Product Characteristics.

FERRIPROX DOSE TABLE (100 MG/ML ORAL SOLUTION)

Supporting information

An oral treatment with flexible dosing[1]

Ferriprox is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg. Dose per kilogram body weight should be calculated to the nearest 2.5 ml for the oral solution

To obtain a dose of about 75 mg/kg/day, use the volume of oral solution suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed

Dose table for Ferriprox 100 mg/ml oral solution

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/ day)	ml of oral solution (three times/day)
20	1500	500	5.0
30	2250	750	7.5
40	3000	1000	10.0
50	3750	1250	12.5
60	4500	1500	15.0
70	5250	1750	17.5
80	6000	2000	20.0
90	6750	2250	22.5

Ferriprox is available as: 500 mg and 1000 mg tablets and an oral solution 100 mg/ml[1]

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions; chronic administration of more than 2.5 times the maximum recommended dose has been associated with neurological disorders

It is recommended that serum ferritin concentrations or other indicators of body iron overload be monitored every 2-3 months after starting Ferriprox. Dose adjustments should be tailored to the individual patient's response and therapeutic goals. Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l

1. Ferriprox Summary of Product Characteristics

Prescribing information

Abbreviated Prescribing Information – Denmark

Forkortet produktresumé for Ferriprox (deferipron) 500 mg filmovertrukne tabletter, 1000 mg filmovertrukne tabletter, 100 mg/ml oral opløsning

Indikationer: Ferriprox monoterapi er indiceret til behandling af jernophobning hos talassæmi-patienter, hvor nuværende kelationsterapi er kontraindiceret eller utilstrækkelig. Ferriprox i kombination med et andet kelerende stof er indiceret til behandling af talassæmi-patienter, hvor monoterapi med et andet jernkelerende stof er utilstrækkelig eller hvor forebyggelse eller behandling af livstruende konsekvenser af jernophobning (hovedsagelig i hjertet) kræver hurtig eller intensiv korrektion. **Dosering:** Deferipron-behandling bør indledes og opretholdes af en læge, der har erfaring i behandling af patienter med talassæmi. Deferipron indgives som regel oralt med 25 mg/kg legemsvægt tre gange dagligt for en total daglig dosis på 75 mg/kg legemsvægt. Se produktresumé pkt. 4.2 for anbefalede doser for legemsvægt i 10 kg trin. En total daglig dosis på over 100 mg/kg kropsvægt kan ikke anbefales, da der muligvis er en øget risiko for bivirkninger. Koncentrationerne af serumferritin eller andre indikatorer for jernophobning bør overvåges hver 2. til 3. måned. Dosisjusteringer bør skræddersys til de enkelte patienters respons og terapeutiske mål. Afbrydelse af behandling bør overvejes, hvis serumferritin falder under 500 µg/l. Hvis monoterapi er utilstrækkelig, kan Ferriprox anvendes sammen med deferoxamin med en standarddosis (75 mg/kg/dag), men bør ikke overstige 100 mg/kg/dag. I tilfælde af jerninduceret hjertesvigt bør Ferriprox med 75-100 mg/kg/dag tilføjes til behandlingen med deferoxamin. Samtidig brug af jernkelerende stoffer frarådes, hvis serumferritin falder under 500 µg/l. **Kontraindikationer:** Overfølsomhed over for det aktive stof eller over for et eller flere af hjælpestofferne. Tidligere gentagen forekomst af neutropeni. Tidligere forekomst af agranulocytose. Graviditet. Amning. Da mekanismen for neutropeni fremkaldt af deferipron ikke er kendt, bør patienterne ikke indtage medicin, der vides at være forbundet med neutropeni, eller medicin, der kan medføre agranulocytose. **Advarsler og forsigtighedsregler:** Deferipron har vist sig at forårsage neutropeni, herunder agranulocytose. Patientens absolutte neutrofiltal (ANC) skal kontrolleres hver uge under det første års behandling. Agranulocytose og neutropeni forsvinder normalt, når behandlingen seponeres, men der har været tilfælde af agranulocytose med dødelig udgang. Hvis patienten får en infektion, skal behandlingen omgående seponeres, og ANC skal kontrolleres hurtigst muligt. Neutrofiltallet skal derefter kontrolleres hyppigere. Behandling med deferipron bør ikke indledes, hvis patienten har neutropeni eller svækket immunforsvar. Risikoen for agranulocytose og neutropeni er højere, hvis ANC i udgangspunktet er mindre end 1,5 x 10^9/l. I tilfælde af neutropeni kan fornyet behandling ikke anbefales. I tilfælde af agranulocytose er fornyet behandling kontraindiceret. En carcinogen virkning af deferipron kan ikke udelukkes. Det anbefales at kontrollere plasma Zn^{2+} koncentrationen og tilføre ekstra i tilfælde af mangel. Der skal udvises forsigtighed hos patienter med nyresygdom i slutstadiet eller svær nyreinsufficiens. Ved vedvarende forøgelse af ALAT bør det overvejes at seponere behandlingen. Hos talassæmi-patienter er der en forbindelse mellem leverfibrose og jernophobning og/eller hepatitis C. Der skal udvises særlig forsigtighed for at sikre, at jernkeleringen hos patienter med hepatitis C er optimal, og leverhistologien bør monitoreres nøje. Der kan ses rødlig/brunlig misfarvning af urinen. Neurologiske forstyrrelser er observeret hos børn. Anvendelse af deferipron bør ophøre, hvis der observeres neurologiske forstyrrelser. Dødsfald og livstruende situationer (forårsaget af agranulocytose) er rapporteret med deferipron i kombination med deferoxamin. Ferriprox oral opløsning indeholder farvestoffet Sunset Yellow (E110), som kan forårsage allergiske reaktioner. **Interaktion med andre lægemidler og andre former for interaktion:** Da deferipron binder sig til metalkationer, er der mulighed for interaktioner mellem deferipron og trivalente kationafhængige lægemidler, såsom aluminium-baserede antacida, og samtidig brug kan derfor ikke anbefales. Baseret på de rapporterede utilsigtede interaktioner mellem deferoxamin og C-vitamin bør der udvises forsigtighed ved samtidig indgivelse. **Bivirkninger:** *Meget almindelige:* kvalme, abdominalsmerter, opkastning, kromaturi. *Almindelige:* neutropeni, agranulocytose, øget appetit, hovedpine, diarré, artralgi, træthed, forhøjede leverenzymer. *Hyppighed ikke kendt*: overfølsomhedsreaktioner, udslæt, urticaria. I tilfælde af en overdosering er tæt lægelig supervision af patienten nødvendig. **Overdosering:** I tilfælde af en overdosering er tæt lægelig supervision af patienten nødvendig. **Pakningsstørrelser:** *500 mg filmovertrukne tabletter:* 100 stk. *1000 mg filmovertrukne tabletter:* 50 stk. *Oral opløsning*: 1 flaske med 250 ml eller 500 ml. **Priser:** Se dagsaktuelle priser på www.medicinpriser.dk. **Udlevering:** BEGR. **Generelt tilskud:** Nej. **Indehaver af markedsføringstilladelsen:** Chiesi Farmaceutici S.p.A., Italien. **Lokal repræsentant:** Chiesi Pharma AB, Sverige, tlf.: + 46 8 753 35 20, e-post: infonordic@chiesi.com.
Denne produktinformation er omskrevet/forkortet i forhold til det af Det Europæiske Lægemiddelagentur godkendte produktresumé dateret 4. maj 2020. Produktresumeet kan vederlagsfrit rekvireres fra indehaveren af markedsføringstilladelsen eller dennes repræsentant eller findes på Det Europæiske Lægemiddelagenturs hjemmeside: http://www.ema.europa.eu/ema/. Læs produktresuméet før ordination, især med hensyn til dosering, bivirkninger, advarsler og kontraindikationer.
Revisionsdato: 5. november 2020

Prescribing information

Abbreviated Prescribing Information – Norway

Ferriprox (deferipron)

Jernbindende middel. ATC-nr.: V03A C02. Utleveringsgruppe C. Reseptbelagt legemiddel. Kan forskrives på H-resept.

TABLETTER, filmdrasjerte *500 mg og 1 g.*
MIKSTUR, oppløsning *100 mg/ml.*
Indikasjoner: Som monoterapi til behandling av jernoverskudd hos pasienter med thalassemia major når nåværende kelateringsbehandling er kontraindisert eller utilstrekkelig. I kombinasjon med en annen kelator (se Forsiktighetsregler i SPC) hos pasienter med thalassemia major når monoterapi med jern-kelator er ineffektiv, eller når forebygging eller behandling av livstruende konsekvenser forbundet med jernoverskudd (hovedsakelig overbelastning av hjertet), berettiger rask eller intensiv korreksjon. **Dosering:** Behandling skal initieres og vedlikeholdes av lege med erfaring innen behandling av talassemi. *Normal dose:* 25 mg/kg kroppsvekt 3 ganger daglig (morgen, midt på dag og om kvelden). Dose pr. kg kroppsvekt skal beregnes til nærmeste 1/2 tablett eller 2,5 ml mikstur. Se anbefalte daglige doser for kroppsvekt med 10 kg intervaller i dosetabell i SPC. Doser >100 mg/kg/dag anbefales ikke pga. potensiell økt risiko for bivirkninger. Kronisk administrering av >2,5 × maks. anbefalt dose er forbundet med nevrologiske lidelser. For å vurdere behandlingseffekt bør serumferritinkonsentrasjon eller andre indikatorer på jernmengde måles hver 2.-3. måned. Seponering skal vurderes ved serumferritin <500 µg/liter. Kan brukes sammen med deferoksamin ved standarddosen (75 mg/kg/dag) når monoterapi er utilstrekkelig, men bør ikke overstige 100 mg/kg/dag. Ved jernindusert hjertesvikt bør 75-100 mg/kg/dag tilsettes deferoksamin-behandlingen. Se SPC for deferoksamin. Samtidig bruk av jern-kelatorer anbefales ikke ved serumferritin <500 µg/liter pga. fare for overdreven fjerning (kelatering) av jern. **Kontraindikasjoner:** Overfølsomhet for innholdsstoffene. Tilbakevendende episoder med nøytropeni eller agranulocytose. Graviditet eller amming. Samtidig bruk av legemidler kjent for å ha tilknytning til nøytropeni eller som kan forårsake agranulocytose må unngås, pga. ukjent mekanisme for deferipronindusert nøytropeni. **Forsiktighetsregler:** *Nøytropeni/agranulocytose:* Deferipron kan forårsake nøytropeni, inkl. agranulocytose (se Bivirkninger i SPC). Nøytrofiltall bør overvåkes ukentlig. Ved infeksjon må preparatet seponeres og nøytrofiltallet kontrolleres oftere. Pasienten må rådes til å umiddelbart informere lege ved symptomer på infeksjon. Det anbefales at behandlingsprotokoll er på plass før deferipronbehandling startes. *I tilfelle nøytropeni:* Seponer umiddelbart deferipron og alle andre legemidler med potensiale til å forårsake nøytropeni. Pasienten skal rådes til å begrense kontakten med andre personer for å redusere infeksjonsfaren. Se foreslått behandling av nøytropeni i SPC. *I tilfelle alvorlig nøytropeni eller agranulocytose:* Følg retningslinjene i SPC samt hensiktsmessig behandling som G-CSF («granulocyte colony stimulating factor»), som startes samme dag som hendelsen identifiseres. Gis daglig til tilstanden forsvinner. Isoler pasienten, og dersom klinisk indisert, legg pasienten inn på sykehus. Ved nøytropeni anbefales ikke ny behandling. Ved agranulocytose er ytterligere behandling kontraindisert. *Karsinogenitet/mutagenitet:* Mht. genotoksisitetsresultatene kan et karsinogent potensiale hos deferipron ikke utelukkes. *Zn^{2+}-konsentrasjon i plasma:* Det anbefales kontroll av Zn^{2+}-konsentrasjon i plasma, og tilskudd av Zn^{2+} i tilfelle defisitt. *Hiv-positive eller andre med nedsatt immunforsvar:* Behandling av pasienter med svekket immunforsvar, skal ikke startes med mindre potensiell nytte overgår potensielle risikoer, da deferipron er assosiert med nøytropeni og agranulocytose. *Nedsatt nyre- eller leverfunksjon og leverfibrose:* Forsiktighet må utvises ved terminal nyresykdom eller alvorlig nedsatt leverfunksjon. Renal og hepatisk funksjon må overvåkes når denne pasientgruppen behandles med deferipron. Spesiell forsiktighet skal utvises for å sikre at behandlingen gir optimal effekt. Nøye overvåkning av leverhistologi anbefales. *Misfarging av urin:* Urinen kan bli rødaktig/brun pga. utskillelsen av jern-deferipronkomplekset. *Nevrologiske lidelser:* Nevrologiske lidelser er observert hos barn behandlet med >2,5 ganger maks. anbefalt dose i flere år, men også ved standarddoser. Bruk av doser >100 mg/kg/dag anbefales ikke. Bør seponeres dersom nevrologiske lidelser observeres. *Kombinert bruk med andre jern-kelatorer:* Kombinasjonsbehandling bør vurderes individuelt. Respons skal vurderes med jevne mellomrom og bivirkninger overvåkes nøye. Dødsfall og livstruende situasjoner (forårsaket av agranulocytose) har forekommet med deferipron i kombinasjon med deferoksamin. Nøye overvåkning av hjerteproblemer er påkrevd ved kombinasjonsbehandling. *Hjelpestoff:* Ferriprox mikstur inneholder fargestoffet paraoransje (E110), som kan forårsake allergiske reaksjoner. **Interaksjoner:** For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse på felleskatalogen.no. Samtidig inntak av aluminiumbaserte antacida og deferipron anbefales ikke. Basert på rapportert negativ interaksjon som kan oppstå mellom deferoksamin og C-vitamin, må det utvises forsiktighet når deferipron og C-vitamin gis samtidig. **Graviditet og amming:** *Graviditet:* Fertile kvinner må rådes til å unngå graviditet pga. legemidlets klastogene og teratogene egenskaper. Disse kvinnene må rådes til å bruke prevensjon, og umiddelbart slutte å ta deferipron ved graviditet, eller planlagt graviditet. *Amming:* Skal ikke brukes under amming. Dersom behandling ikke kan unngås, må ammingen opphøre. **Bivirkninger:** *Svært vanlige (≥1/10):* Gastrointestinale: Abdominalsmerte, kvalme, oppkast. Nyre/urinveier: Kromaturi. *Vanlige (≥1/100 til <1/10):* Blod/lymfe: Agranulocytose, nøytropeni. Gastrointestinale: Diaré (for det meste mild og forbigående). Generelle: Fatigue. Muskel-skjelettsystemet: Artralgi. Nevrologiske: Hodepine. Stoffskifte/ernæring: Økt appetitt. Undersøkelser: Økte leverenzymer (asymptomatisk og forbigående hos de fleste og returnerte til baseline uten seponering eller dosereduksjon). **Pakninger og priser:** *Tabletter: 500 mg:* 100 stk.[1] (flaske) kr 2446,60. *1 g:* 50 stk.[1] (flaske) kr 2446,60. *Mikstur:* 500 ml[1] (flaske m/målekopp) kr 2233,10. **Refusjon:** *1. H-resept: V03A C02_13. Deferipron*
Refusjonsberettiget bruk: Der det er utarbeidet nasjonale handlingsprogrammer/nasjonal faglig retningslinje og/eller anbefalinger fra RHF/LIS spesialistgruppe skal rekvirering gjøres i tråd med disse. *Vilkår:* (216) Refusjon ytes kun etter resept fra sykehuslege eller avtalespesialist. (222) En blå resept kan ekspederes med H-resept som hjemmel hvis resepten er forskrevet før legemiddelet ble overført til H-reseptordningen.
Basert på SPC godkjent av SLV/EMA: 04.05.2020.
Innehaver av markedsføringstillatelsen: Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma, Italia. *Lokal repr.:* Chiesi Pharma AB. Telefon: 00 46 8 753 35 20, e-post: medinfonordic@chiesi.com. www.chiesi.no.

Les felleskatalogtekst eller preparatomtalen (SPC) for mer informasjon, se www.felleskatalogen.no

Sist endret: 02.11.2020.

Prescribing information

Abbreviated Prescribing Information – Sweden

Ferriprox (deferipron), 500 mg och 1000 mg, filmdragerade tablett, samt 100mg/ml, oral lösning. Rx. F. ATC-kod: V03AC02 Medel vid järnförgiftning, kelatkomplexbildare. **Indikation:** Ferriprox som monoterapi är indicerad för behandling av järnöverskott hos patienter med thalassaemia major då gängse terapi med kelatkomplexbildare är kontraindicerad eller otillräcklig. Ferriprox i kombination med en annan kelatkomplexbildare är indicerad hos patienter med thalassaemia major då monoterapi med järnkelatkomplexbildare är ineffektiv, eller då prevention eller behandling av livshotande följder av järnöverskott (huvudsakligen överbelastning av hjärtat) motiverar snabb eller intensiv korrigering. **Kontraindikationer:** Överkänslighet mot det aktiva innehållsämnet eller mot något hjälpämne. Tidigare återkommande neutropeniepisoder. Tidigare agranulocytos. Graviditet. Amning. På grund av den okända mekanismen hos deferiproninducerad neutropeni, får patienterna inte ta medicinska produkter som man vet har samband med neutropeni eller sådana som kan orsaka agranulocytos. **Varningar och försiktighet:** Deferipronbehandling bör påbörjas och handhas av en läkare med erfarenhet av behandling av patienter med talassemi. Behandling med deferipron skall inte initieras om patienten lider av neutropeni. Deferipron har visat sig orsaka neutropeni, inklusive agranulocytos. Patientens absoluta neutrofilantal (absolute neutrophil count, ANC) ska övervakas varje vecka under det första behandlingsåret. För patienter vars Ferriprox inte har avbrutits under det första behandlingsåret på grund av minskning av neutrofilantalet, kan frekvensen på ANC-övervakning förlängas till patientens blodtransfusionsintervall (varannan till var fjärde vecka) efter ett år med deferipronbehandling. Patienterna ska vara medvetna om att de ska kontakta sin läkare om de upplever symptom som indikerar infektion (såsom feber, halsont och influensaliknande symtom). Avbryt omedelbart deferipron om patienten upplever infektion. Förslag till behandling av fall av neutropeni finns i produktresumén. Det rekommenderas att en sådan behandlingsplan utarbetas innan behandling med deferipron påbörjas. Med tanke på de genotoxiska resultaten kan man inte utesluta möjligheten att deferipron kan vara karciogent. Övervakning av plasma Zn^{2+}-koncentrationen, samt supplementering om brist föreligger, rekommenderas. Med tanke på att deferipron kan associeras med neutropeni och agranulocytos bör man inte påbörja behandling av patienter med nedsatt immunförsvar såvida inte de möjliga fördelarna överväger de möjliga riskerna. Försiktighet måste iakttas när det gäller patienter med njursjukdom i slutstadium eller med allvarlig leverdysfunktion. Njur- och leverfunktion ska följas upp hos dessa patientgrupper under deferipronbehandling. Man måste noga försäkra sig om att järnkelatbildningen hos patienter med hepatit C är optimal. Hos dessa patienter rekommenderas en noggrann övervakning av leverhistologin. Patienterna bör informeras om att deras urin kan få en rödaktig/brun missfärgning beroende på utsöndringen av järndeferipronkomplexet. Neurologiska störningar har setts hos barn som behandlats med mer än 2,5 ggr den maximala rekommenderade dosen under flera år, men har även observerats vid standarddoser av deferipron. Förskrivande läkare bör komma ihåg att användningen av doser över 100 mg/kg/dag inte rekommenderas. Användning av deferipron bör avbrytas om neurologiska störningar observeras. Användning av kombinationsterapi bör övervägas från fall till fall. Terapiresponsen bör utvärderas regelbundet, och förekomsten av biverkningar följas upp noggrant. Dödsfall och livshotande situationer har rapporterats med deferipron i kombination med deferoxamin. Kombinationsterapi med deferoxamin rekommenderas inte då monoterapi med någon av kelatkomplexbildarna är tillräcklig eller då S-ferritinvärdet sjunker under 500 µg/l. Ferriprox oral lösning innehåller färgämnet para-orange (E110) som kan orsaka allergiska reaktioner. *Interaktioner med andra läkemedel och övriga interaktioner:* Samtidigt bruk av aluminiumbaserade syraneutraliserande medel och deferipron rekommenderas inte. Med tanke på den rapporterade ogynnsamma interaktion som kan uppträda mellan deferoxamin och vitamin C, bör man vara försiktig vid samtidig tillförsel av deferipron och vitamin C. *Graviditet:* Kvinnor i fertil ålder måste rådges att undvika graviditet eftersom läkemedlet har klastogena och teratogena egenskaper. Dessa kvinnor ska rådges att använda preventivmedel och att omedelbart sluta ta deferipron om de blir gravida eller planerar att bli gravida. *Amning:* Deferipron får inte användas av ammande mödrar. Om behandling inte kan undvikas måste amningen upphöra. **Kontakt:** Chiesi Pharma AB, Klara Norra Kyrkogata 34, 111 22 Stockholm. Telefon: 08-753 35 20, e-post: infonordic@chiesi.com. För mer information och pris, se www.fass.se. **Senaste datum för översyn av produktresumén:** 2021-03-15.

FERRIPROX: TOTAL IRON CHELATION MANAGEMENT IN TM

Summary

Ferriprox: As monotherapy and/or in combination in TM

Efficacy

- Proven to increase survival vs DFO[1,2]
- Most effective at reducing cardiac iron burden compared with DFO or DFX[3]
- Proven to reduce iron levels in the heart, liver and serum ferritin[2,4]

Manageable tolerability

- Ferriprox has a manageable tolerability profile[2]

Dosing

- Reduced pill burden and choice of formulations[2]
- Possible 2–4 weekly monitoring after 1 year of treatment[2]
- No dosage adjustment required in mild-to-severe renal impairment or mild-to-moderate hepatic impairment[2]

1. Maggio A, et al. Blood Cells Mol Dis. 2009;42(3):247-51.
2. Ferriprox Summary of Product Characteristics.
3. Pennell D, et al. Blood. 2006;107(9):3738-3744.
4. Tanner MA, et al. Circulation. 2007;115(14):1876-84.

DFO= deferoxamine.
DFX = deferasirox.
TM = thalassaemia major.

268-2021-MARK, September 2021

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chiesipharma.se | chiesipharma.dk | chiesi.fi | chiesi.no

Chiesi
global rare diseases