THALASSEMIA

CHI Formulary Indication Review

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Council of Health Insurance

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Table of Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete Blood Count
CHI	Council of Health Insurance
DFO	Deferoxamine
DFP	Deferiprone
DFX	Deferasirox
Dw	Dry weight
HAS	Haute Autorité de Santé
Hb	Hemoglobin
Hb A	Adult Hemoglobin
Hb F	Fetal Hemoglobin
HPLC	High-Performance Liquid Chromatography
HSCT	Hematopoietic stem cell transplantation
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
LIC	Liver Iron Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NTDT	Non-Transfusion-Dependent Thalassemia
PBAC	Pharmaceutical Benefits Advisory Committee
RBC	Red Blood Cell
SF	Serum ferritin
TDT	Transfusion-Dependent Thalassemia
TIF	Thalassemia International Federation
WBC	White Blood Cell
WT	Weight

Executive Summary

Thalassemia is a group of inherited disorders that arise as a result of certain mutations in hemoglobin (Hb) genes, affecting the makeup of Hb in the red blood cells, which leads to certain pathophysiological disorders. The genetic disorder is characterized by the absolute or partial synthesis of one or more alpha (α)- or beta (β)- globin chains.

Alpha thalassemia occurs when some or all of the 4 genes that make hemoglobin (the alpha-globin genes) are missing or damaged.

There are 4 types of alpha thalassemia:

- **Alpha thalassemia silent carrier:** one gene is missing or damaged, and the other 3 are normal. Blood tests are usually normal. Your red blood cells may be smaller than normal.
- **Alpha thalassemia carrier:** two genes are missing. You may have mild anemia.
- **Hemoglobin H disease:** three genes are missing. This leaves just 1 working gene. You may have moderate to severe anemia. Symptoms can worsen with fever. They can also get worse if you are exposed to certain medicines, chemicals, or infectious agents. Blood transfusions are often needed. You have a greater risk of having a child with alpha thalassemia major.
- **Alpha thalassemia major:** all 4 genes are missing. This causes severe anemia. In most cases, a baby with this condition will die before birth.

Delta-thalassemia is due to mutation of the genes responsible for synthesis of the delta chain. A mutation that prevents formation of the delta chain is called delta^0, and if some delta chain is formed, the mutation is called delta$^+$. If an individual inherits two delta^0 mutations, no delta chain is produced and no HbA_2 can be detected in the blood (normal level<3.5%). However, if an individual inherits two delta$^+$ mutations, a decrease in HbA_2 is observed. All patients with delta-thalassemia have normal hematological consequences although the presence of the delta mutation can obscure diagnosis of the beta-thalassemia trait because in beta-thalassemia, HbA_2 is increased but the presence of delta may reduce HbA_2 concentration, thus masking diagnosis of the beta-thalassemia trait.

The types of **β-thalassemia** are called major, intermedia, and minor. β-Thalassemia major is caused by a defect in 2 genes that leads to absence or a severe decrease in β-globin synthesis. β-Thalassemia intermedia is a clinical phenotype with moderate anemia and transfusion independence. Genetically it results from mutations in the 2 β genes resulting in mild to moderate decrease in their synthesis. β-Thalassemia minor, or thalassemia trait, occurs when the defect is present in only 1 gene.[1]

β-Thalassemia comprises a complex spectrum of clinical presentations. The clinical phenotype is influenced by the genetic phenotype and other modifiers. The basic disease is caused by the inability to produce normal β-globin chain with the consequence of excess α-chain, leading to disruption of the α:β ratio, which in turn will cause various cellular and clinical syndromes.[1]

β-Thalassemia is clinically classified into 4 subtypes:

1. β-thalassemia silent carriers; asymptomatic, one β-globin chain is normal, and the other is partially defective (ββ+).
2. β-thalassemia trait; one β-chain is totally defective, and the other is normal (ββ°). These patients have mild anemia, and < 20% have palpable spleen.
3. β-thalassemia intermedia; this term is useful clinically but does not correlate with its genetic or clinical mechanism for the phenotype. Usually used to describe β-thalassemia patients who do not require chronic red cell transfusion in early childhood, although by the second decade of life they may present the same picture as β-thalassemia major. Most of the patients have homozygous partial production defect of β globin $\beta^+\beta^+$ or $\beta^+\beta^\circ$, and there are many co-inheritance factors that influence the clinical spectrum. These patients have a spectrum of severity, but all have complications in common:
    a. Chronic anemia: high cardiac output, increased pulmonary vascular resistance, pulmonary hypertension, and heart failure.
    b. Iron overload: because the patients are not receiving chronic transfusion, there is increased gut iron absorption with subsequent symptoms and signs of iron overload.
4. β-thalassemia major (transfusion-dependent β- thalassemia); total impairment of β-globin chain production leading to excess α-globin chain, which in turn is unable to form soluble tetramers and is precipitated in the cell, leading to a sequence of cellular and clinical events. These patients are well at birth, and the clinical picture will start after the fetal Hb (Hb F) switch to adult Hb (Hb A) fails because there is no β-chain produced, leading to anemia, which usually starts after 6 months of age. The severity of phenotype is heterogeneous depending on the type of mutation influencing the β-chain production, e.g., β°, β^+, the balance between α- and β-chain and Hb F production. The manifestations in untreated patients include pallor, irritability, cardiac failure, growth failure, hepato-splenomegaly, bone abnormality, and features of hemolysis. Most untreated patients under the age of 5 years die due to anemia, heart failure, or infections.[1]

β-Thalassemia carriers comprise 1.5% of the worldwide population, with an estimated 60,000 infants with a serious defect being born every year. In the United States, approximately 1,000 individuals have β-thalassemia major, the most severe form of thalassemia. It is most found in people of Mediterranean descent, such as Italians and Greeks, but also affects people from other parts of the world such as Africa, the Middle East, the Indian subcontinent, and Southeast Asia.[1]

The incidence of β-thalassemia in Arabian Gulf countries is not clearly known due to lack of mandatory screening programs. The majority of data were obtained from scattered screening studies using Hb electrophoresis as summarized in **Table 1.**

Table 1. Estimated Prevalence of β-Thalassemia (Minor and Major) in Arabian Gulf Countries

Country	Minor (%)	Major (%)
Saudi Arabia	3.4	Not available
Bahrain	0.88	0.16
Qatar	28	0.07
United Arab Emirates	1.7	Not available
Oman	2	0.04

This report compiles all clinical and economic evidence related to Thalassemia according to the relevant sources. The ultimate objective of issuing Thalassemia guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients with thalassemia in Saudi Arabia**. The main focus of the review was on KSA, North American and European, and other international guidelines issued within the last ten years.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in thalassemia were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of thalassemia.

In general, the recommended treatment for thalassemia major involves lifelong, regular **blood transfusions**, usually administered every 2 to 5 weeks to maintain the pre-transfusion Hb level above 9.5-10.5 g/dL.

During the introduction of a regular transfusion program in the early 1960s, an iron chelating agent demonstrated improved survival. There are 3 main available chelators are deferoxamine, deferiprone, and deferasirox. In November 2019, the Food and Drug Administration (FDA) approved the hematopoietic agent luspatercept for the treatment of anemia in patients with beta-thalassemia who require regular red blood cell transfusions.

In November/December 2023, **Exagamglogene Autotemcel** was approved by the FDA for the management of sickle cell disease, and by the EMA and MHRA for the treatment of both sickle cell disease and transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom hematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.[2–4] In January 2024, the SFDA approved Exagamglogene Autotemcel as a breakthrough therapy for TDT for patients who do not have appropriate matched donor for HSCT, however, it is currently not registered by the SFDA.[5]

Major recommendations for suggested drug therapies are summarized in the table below:

Table 2. SFDA-Registered Drugs for the Management of Thalassemia

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Deferoxamine	Iron overload in thalassemia	**1st**	N/A	N/A
Deferiprone	Iron overload in thalassemia	**1st**	N/A	Positive Recommendation from CADTH Negative recommendation from HAS
Deferasirox	Iron overload in thalassemia	**1st**	N/A	Positive Recommendation from CADTH

Luspatercept	Beta-thalassemia transfusion-dependent and experience complications associated with chronic transfusions	**2nd**	N/A	Positive Recommendation from CADTH Negative recommendation from HAS

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

1.1.1 Regional Consensus Opinion for the Management of Beta Thalassemia Major in the Arabian Gulf Area (*Orphanet J Rare Dis*., 2013)

This regional consensus was published in 2013 in the Orphanet Journal of Rare Diseases and was developed for the diagnosis, treatment, and follow-up of beta thalassemia.[1]

Diagnosis of beta thalassemia:

The diagnosis of β-thalassemia requires a patient history, physical examination, and confirmatory laboratory tests including complete blood count and blood film morphology, both demonstrating microcytic hypochromic anemia, and confirmation by alkaline Hb electrophoresis (**Table 3**).

Table 3. The Phenotypes and Genotypes of β-Thalassemia

Phenotypes	Genotypes	MCV	Anemia	Hb electrophoresis
Silent carrier	$\beta\beta^{+}$	Low/Normal	None	Normal
Minor (trait)	$\beta\beta^{o}$	Low	Mild	High Hb A_2
Intermedia	$\beta^{+}\beta^{+}$ and others	Low	Moderate	Presence of small amount of A and could be similar to Major
Major	$\beta^{o}\beta^{o}$	Low	severe	Hb A absent, only Hb A_2 and Hb F are present

HB hemoglobin, **Hb A** adult hemoglobin, **Hb F** fetal hemoglobin, **MCV** mean corpuscular volume

The features of the different presentations of thalassemia syndromes are:

1. β-thalassemia silent carrier:
    - Normal phenotype
    - Laboratory: normal Hb, RBC indices, and Hb electrophoresis

2. β-thalassemia minor (trait)
    - Hematocrit >30%
    - Hb and peripheral morphology similar to iron deficiency state
    - RBC count more than normal, MCV is low.
    - RDW is normal.
    - Hb electrophoresis or HPLC show elevated Hb A2 (except in rare cases will be normal)
3. β-thalassemia intermedia
    - Hb is low (6-10 g/dL)
    - CBC and peripheral morphology are variable with hypochromic, microcytic changes with variation in RBC size and shape.
    - RDW is increased.
    - Hb electrophoresis or HPLC show different patterns; some patients are able to produce Hb A in small quantities or similar to homozygous β-thalassemia zero where Hb A is absent.
4. β-thalassemia major
    - CBC:
        - False elevated WBC because of nucleated RBC
        - Severe anemia with Hb as low as 3-4 g/dL
        - Microcytic hypochromic picture with fragmented RBC, tear drops, target cells, and RBC with inclusion bodies.
    - Reticulocyte count low.
    - Serum iron to TIBC is high.
    - Hb electrophoresis: absent Hb A with remaining as Hb F and Hb A2 (**Table 3**)

The final step in a diagnostic approach is to perform DNA studies on the genetic material extracted from peripheral blood. This will identify the type of the mutation and help identify the silent carriers.

Treatment of beta thalassemia major

1. **<u>Transfusion therapy in thalassemia</u>**

Red cell transfusions are required to increase the oxygen-carrying capacity of the blood through raising the Hb concentration of patients with acute or chronic anemia. Guidelines for the transfusion of blood and blood components and the

management of transfused patients are in accordance with the British Committee for Standards in Hematology. The major goals for blood transfusion therapy include:

i. Maintenance of red cell viability and function during storage to ensure sufficient transport of oxygen.

ii. Use of donor erythrocytes with a normal recovery and half-life in the recipient

iii. Achievement of appropriate Hb level

iv. Avoidance of adverse reactions, including transmission of infectious agents.

Current practice and recommendation for transfusion therapy in Arabian Gulf countries

- The recommended treatment for thalassemia major involves lifelong, regular blood transfusions, usually administered every 2 to 5 weeks to maintain the pre-transfusion Hb level above **9.5-10.5 g/dL**. However, in most of the Gulf countries, 9 g/dL is accepted as the minimum pre-transfusion Hb level. Higher levels (11–12 g/dL) may be needed for patients with cardiac complications.
- The post-transfusion Hb is kept not higher than 14–15 g/dL.
- The current practice includes extended red cell antigen typing of patients including C, E, and Kell before the first transfusion. At each transfusion, we do a full cross match and screening for the new antibodies. Matching for C, E, and Kell antigens is only done for negative patients. The blood is leuko-reduced with pre-storage filtrations. Some countries also practice bed-side filtrations. Transfusion is attended by nurses who report any adverse reactions.
- Blood that has not been transfused by 4 hours after hooking is discarded.

Iron overload

- During the introduction of a regular transfusion program in the early 1960s, an iron chelating agent demonstrated improved survival. However, iron overload is still one of the most critical issues, and its complications remain the most important cause of morbidity mortality. In addition, the lack of adherence to an iron chelating agent regimen is considered an important factor in suboptimal clinical improvement and poor prognosis.
- In a chronically transfused patient, one unit of blood contains 200 mg iron. Since humans have no physiologic mechanism for active elimination of excess iron, patients receiving regular RBC transfusions develop cumulative iron overload and are at risk for iron toxicity.

- In addition to the transfused iron, thalassemia patients absorb more iron than normal individuals. The mechanism of increased absorption in thalassemia patients is thought to be related to paradoxical Hepcidin suppression from dys-erythropoiesis. Free iron is subsequently deposited primarily in parenchymal cells of different organs. Then it will participate in oxidative reactions to generate free oxygen radicals, which can lead to chronic cell toxicity and DNA damage.

Measurements of iron load

Parameters used to monitor iron load include serum ferritin, liver biopsy, and MRI assessment of liver and cardiac iron, in conjunction with functional testing such as echocardiography, liver function test, and measures of endocrine function.

- **Serum ferritin**

Serum ferritin is the most commonly used parameter for monitoring iron overload despite its inaccuracy and limitation in assessing the body iron overload. It is a valuable method to roughly assess the long-term, overall status of iron overload and to monitor response to chelation therapy. It is also valuable due to its ease of measurement and wide availability, and it correlates with cardiac impairment and survival but not with hepatic iron. Serum ferritin is elevated in many other conditions such as infections, inflammation, or malignancy. Iron overload is generally defined as serum ferritin consistently ≥ 1000 ng/L. It is recommended to know the baseline level of ferritin and to assess the trend by taking serial measurement of serum ferritin every 3 months. In the Gulf area, due to the wide availability of the test in all treating centers, the test is done on a monthly basis.

- **Liver biopsy**

Liver iron concentration remains the most accurate measure of total body iron loading, and liver biopsy was previously considered to be the gold standard of liver iron assessment, but is an invasive procedure associated with a risk of complications. Liver biopsy is still performed to evaluate liver fibrosis, cirrhosis, or hepatocellular carcinoma, which are possible complications in all patients with liver iron overload. It is well known that a hepatic iron level of 7–15 mg/g dry weight is associated with an increased risk of complications; a higher level increases risk of cardiac disease and early death. However, because of its invasive nature and lack of cultural acceptance, this test is rarely performed in the Gulf area centers.

- **MRI assessment of liver iron**

MRI is the method of choice in the monitoring of various organs' iron levels where the measurement of tissue proton transverse relaxation rates (R2) was shown to have excellent correlation with liver iron concentration measured by biopsy. An annual monitoring of R2 MRI is recommended, which can be extended to every 2

years for patients with normal liver iron or at the lower end of the ideal iron range of less than 7 mg/g dry weight. Additionally, liver iron levels should also be correlated with standard liver function tests.

– **MRI assessment of cardiac iron**

Similar to liver iron measurement, MRI has been widely used to annually monitor iron levels in the heart where the measurements of T2*, a relaxation parameter intrinsic to protons placed in the magnetic field, is utilized. In the Gulf region, very few centers have this tool available. It is recommended to expand this service for thalassemia patients because MRI is a noninvasive, reliable, and accurate method of assessing iron overload.

2. <u>Chelating agents</u>

- There are 3 main available chelators: **deferoxamine**, **deferiprone**, and **deferasirox** (**Table 4**).
- Deferiprone and deferasirox are oral chelators that have come into the clinic in recent years. They are different in molecular weight, leading to differences in intestinal absorption.
- For several decades, the only available iron chelator was deferoxamine. In the Gulf region, deferoxamine has been available since the early 1970s, and nowadays it is much less widely used except in combined chelation therapy.
- Although the international guidelines recommend the use of deferiprone after the age of 6 years, in some Arabian Gulf countries the syrup formulation has been widely used with good efficacy for children 2 years and above with no serious complications.
- Continued deferiprone therapy during episodes of mild neutropenia (down to 1×109 /L) has not been associated with progression to agranulocytosis. We recommend giving extensive counseling to the patients, with clear instructions to report to hospital emergency in case of fever and to have an urgent CBC with ANC count.
- Deferasirox has been available in the Gulf area since 2007. It has been widely used across all the Gulf countries. Side effects are comparable (**Table 4**) to those published in the literature, and its efficacy has been demonstrated in many clinical trials. It is used only as monotherapy. Some patients do not respond to the maximum dose of 40 mg/kg/day, however, and compliance may be an issue with this drug, just as it is for the other available chelators.

Table 4. Comparative Analysis of Different Iron Chelators. Retrieved from Qari et al. (2013)

	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Brand name	Desferal	Ferriprox	Exjade
Chelator-iron, complex ratio	Hexadentate, 1:1	Bidentate, 3:1	Tridentate, 2:1
Dose (mg/kg/day)	25–50	75–100	20–40
Combination and titration doses (mg/kg/day)	Combination therapy with DFO and DFP, 2 days/week DFO and then continue with DFP		Titration therapy
Administration	Subcutaneous or intravenous, 8–10 hrs/day, 5–7 days/wk	Oral, 3 times daily	Oral, once daily
Plasma half-life (hr)	0.5	2–3	8–16
Route of elimination	Biliary and urinary	Urinary	Biliary
Regulatory approval	US, Canada, Europe, other countries	US, Europe, other countries	US, Canada, Europe, other countries
Indication	Transfusion iron overload and acute iron overload	Transfusion iron overload when DFO is contraindicated or inadequate	Transfusion iron overload
Adverse events	Irritation at the infusion site, ocular and auditory disturbances, growth retardation and skeletal changes, allergy, respiratory distress syndrome with higher doses	Agranulocytosis and neutropenia, gastrointestinal disturbances, arthropathy, increased liver enzyme levels, low plasma zinc level, hepatic fibrosis	Gastrointestinal disturbances, rash, increase in serum creatinine level; potentially fatal renal impairment or failure
Advantage/ Disadvantage	Inexpensive/ Compliance	Route of administration / Compliance	Route of administration / Expensive

3. Hematopoietic stem cell transplantation (HSCT) for thalassemia

- HSCT has the potential to be curative for thalassemia major and has been increasingly adopted, with caution.
- The patient classes have been identified based on 3 risk factors (the Pesaro classification): inadequate iron chelation therapy, presence of liver fibrosis, and hepatomegaly (**Table 5**).

Table 5. Stem Cell Transplantation for Thalassemia

	Class I	Class I	Class III
Number of risk factors	None	1-2	3
Survival (%)	93	87	79
Event free survival (%)	91	83	58
Rejection (%)	2	3	28
Risk of transplant-related mortality (%)	8	15	19
Risk of transplant-related morbidity (%)	9, mainly GVHD	17	22

GVHD: graft-versus-host disease

4. **Future treatment options and prevention**

Stem cell transplantation

Improvement in the life expectancy of patients with β-thalassemia major is due to effective transfusion and iron chelation therapy. However, the only current curative treatment is stem cell transplantation, which is becoming more utilized in good patient candidates, and several centers are doing it in the Gulf States–in particular Saudi Arabia. Production of fetal Hb by cytotoxic agents such as demethylation agents and hydroxyurea has been explored over the last two decades.

Prevention

- Prevention of thalassemia is the only solution to efficiently reduce the huge medical, social, and economic impact in countries where it occurs with high frequency.
- Premarital screening became mandatory for hemoglobinopathies in Saudi Arabia with the intention to decrease the prevalence of the disease.
- Pre-implantation genetic diagnosis is an important option for couples at risk of having children with β-globin mutations.
- Some premarital and antenatal screening centers in the Gulf area refrain from aborting fetuses owing to religious and cultural reasons. Public awareness and related social activities are important tools to improve the understanding of the burden of this disease and of how to support preventive programs aiming to eradicate this disease.

1.2 North American Guidelines

1.2.1 Thalassemia Western Consortium (TWC) Transfusion Management of Beta Thalassemia in the United States (2021)

The most recent American guidelines for the management of beta thalassemia were published in Transfusion in 2021[6]. The following guideline does not provide a specified grade of evidence or level of recommendation. The below recommendations were made:

TRANSFUSION RECOMMENDATIONS FOR β THALASSEMIA

Ever since it was recognized that regular blood transfusions prolong the survival of children with β thalassemia major, there have been efforts to identify patients who should be placed on transfusions. Additional concerns included delineating optimum hemoglobin target and specification of RBC units and creating safe transfusion practices in individuals projected to have a normal life expectancy.

Table 6 summarizes the pathophysiological and clinical features of β thalassemia that underlie these recommendations.

Table 6. Principal Attributes of β-Thalassemia Pertinent to Developing Recommendations for Transfusion Therapy. Retrieved from the TWC 2021 Guidelines.

Features	Impact on transfusion therapy
Disease characteristics	
• Endogenous hemoglobin production is influenced by the severity of β globin mutations, co-inheritance of α thalassemia, and genetic variants linked to HbF production	• Baseline hemoglobin level and tolerance to anemia affect the age at which transfusions are initiated
• Hemoglobin composition (proportion of HbF) alters oxygen affinity of blood and shapes the adaptation to anemia	• These factors influence optimal pre-transfusion hemoglobin level and transfusion frequency for individual patients
• Low hemoglobin level is associated with ineffective erythropoiesis, bone marrow hyperplasia, increased intravascular volume	• Maintain hemoglobin level that averts skeletal changes and extramedullary hematopoiesis
Patient characteristics	
• Anemia leads to poor growth in children and frequent fatigue in adults	• Hemoglobin target may require adjustment in individual patients due to fatigue or pain
• Splenomegaly increases the volume of RBC transfusion necessary to maintain optimal hemoglobin level	• Prevention of splenic enlargement is a goal of transfusion therapy. In non-transfused patients, rapid enlargement of spleen is an indication to initiate transfusions
• Risk of alloimmunization is increased when transfusions are started later in life	• RBC genotype should be obtained at diagnosis for all patients
• Certain complications require modification of transfusion goals	• Higher hemoglobin threshold for patients with heart failure or extramedullary hematopoietic masses
Type of RBC product and matching	
• Disparity of red cell antigens between donors and recipients is greater in a multi-ethnic population	• Risk of alloimmunization is reduced with phenotypic matching. Genotyped donor registry improves access to matched units
• Alloantibodies may be evanescent and antibody screen can become negative with time	• Re-exposure to sensitized antigens can cause hemolytic transfusion reaction
• Transfusion requirements are affected by hemoglobin increment and red cell survival	• Prefer RBC units with higher hemoglobin content, short duration storage, and without irradiation
Other factors	
• Development of transfusional iron overload poses a risk for serious complications	• Use effective chelation regimens to control iron overload instead of lowering pre-transfusion hemoglobin target
• Lack of communication between hospitals increases the risk of transfusion reactions	• Centralized database of patients can prevent the transfusion of inappropriate units

Indications to start regular transfusions

The decision to initiate transfusions attempts to balance consequences from anemia and ineffective erythropoiesis against complications of chronic transfusion therapy.

The paradigm of an infant with severe, symptomatic anemia who requires transfusions for survival served as the historical foundation of transfusion guidelines for β thalassemia major. These high-risk infants have a combination of β^0 and/or

severe β^{+}-globin gene mutations and should be identified through newborn screening.

Nearly 50% of such infants receive their first transfusion by 6 months and 80% by 12 months of age.42 When patients identified through newborn screening have care established before the development of severe symptoms, the time to initiation of transfusions is expected to be shorter. Conversely, when affected individuals preserve significant endogenous hemoglobin synthesis, the decision for starting transfusions can become complex. Such patients have thalassemia intermedia and can survive without being transfused at regular intervals.

The use of splenectomy in children to avoid transfusions has been a particular predicament as the risk of several serious complications becomes manifest only later in adult life. Over the past 3 decades, the long-term consequences of withholding transfusions from patients with severe thalassemia intermedia have become apparent, and this experience is being used to guide the development of the current standards of care. These patients should be seen at 3–4 months intervals to determine whether it is appropriate to continue follow up without transfusions (**Table 7**).

Table 7. Criteria for Initiation of Regular Transfusions

1. Hemoglobin < 7 g/dl on 2 occasions at least 2 weeks apart
   a. β thalassemia major: < 7 g/dl on 2 occasions, with or without symptoms
   b. HbE β thalassemia: < g/dl on 2 occasions and one or more symptom
2. Hemoglobin ≥ 7 g/dl, with one or more of the following symptoms
   a. Growth delay:
      i. Infants (< 2 years): failure to gain weight for 3 months without another etiology
      ii. Children: Height velocity < 3 cm/year
      iii. Delayed onset of puberty: > 12 years in females, > 13 years in males, with endocrine evaluation
   b. Skeletal facial changes: subjective, photographic record, discuss with patient and family
   c. Splenomegaly: Spleen > 6 cm, or enlargement > 1 cm/year after 2 years of age
   d. Extra-medullary hematopoiesis: symptomatic or moderate to severe extramedullary hematopoiesis (EMH)
   e. Cerebrovascular: overt stroke, silent infarcts, arterial narrowing, moya moya
   f. Venous thrombo-embolism

g. Pulmonary hypertension
h. Osteoporotic fracture
i. Poor quality of life in adults: decline in capacity to work or perform usual activities

Hemoglobin target, volume, and rate

The intensity of transfusion therapy for thalassemia is evaluated using the pre-transfusion hemoglobin level. There has been an evolution of the target hemoglobin over the years to balance improvement in anemia and ineffective erythropoiesis with transfusional iron overload.

An adequate pre-transfusion hemoglobin level was initially estimated by improvement in growth and activity in young children, which led to regimens that maintained hemoglobin above 9 or 9.5 g/dl. More intensive regimens that kept the pre-transfusion hemoglobin in the normal range (>12 g/dl) were developed, but concern for greater iron overload from increased blood use prompted moderation of the hemoglobin target.

Prevention of splenomegaly should be the goal of an effective transfusion regimen, thereby mitigating the adverse effects of potential splenectomy.

Another approach to determine the adequacy of transfusions is the suppression of marrow activity, which is achieved by maintaining pre-transfusion hemoglobin between 9 and 10 g/dl. Reticulocyte count does not have a consistent relationship with pre-transfusion hemoglobin, though circulating nucleated red blood cells are suppressed at higher hemoglobin levels. In general, children respond well with mean pre-transfusion hemoglobin 10 g/dl and a range of 9.5–10.5 g/dl, which prevents splenic enlargement and skeletal changes while promoting normal growth.

Individuals with severe β thalassemia intermedia and HbE β thalassemia may initially require only intermittent transfusions, often during an illness causing acute worsening of the baseline level of anemia. The institution of regular transfusions for these groups may be delayed until children are older than 3 years, or even later until adulthood as a response to deteriorating quality of life or complications listed in **Table 7**. Many such patients may tolerate a less intensive regimen using a lower pre-transfusion hemoglobin range of 9–10 g/dl.

The volume of blood transfused is influenced by the interval between transfusions, with those on a 4-week schedule receiving a larger volume compared with those on a 3-week schedule to attain a similar pre-transfusion hemoglobin target. Transfusion volume also depends upon the type of storage solution, since red cell units stored in additive solution have lower hematocrit.

The effect of the pre-transfusion hemoglobin target on the transfusion volume is not clear in the current era where splenectomy is no longer a frequent procedure.

In current practice, when most patients retain their spleen, the pre-transfusion hemoglobin level to achieve the optimal balance between post-transfusion increment and iron loading is not well defined. The interval between transfusions will determine the amplitude of change in hemoglobin from the peak post-transfusion value to the level before the next transfusion.

The rate of blood administration is of great relevance to outpatient RBC transfusion programs, as patients and providers share an interest in the shortest duration of transfusion that is safe. A rate of 5 ml/kg/h has been traditionally used in patients without cardiovascular compromise, which allows transfusions to be completed in a half day. In adults, a rate of administration up to 1 unit per hour can be tolerated.

The volume of transfusion at a single visit is usually limited to a maximum of 20 ml/kg, though higher volumes have been used. These recommendations are summarized in **Table 8**.

Table 8. Recommendations for Hemoglobin Target, Volume, and Rate

1. Target hemoglobin
    a. β thalassemia major: Pre-transfusion hemoglobin of 10.0 g/dl, range 9.5–10.5 g/dl
    b. E β thalassemia: Pre-transfusion hemoglobin of 9–10 g/dl
2. Frequency of transfusion
    a. Every 3 weeks in most older children and adults with β thalassemia major
    b. Every 4 weeks
        i. Younger children with β thalassemia major
        ii. Most children and adults with E β thalassemia
    c. It is preferable to change the volume of blood instead of the interval of transfusion to maintain hemoglobin target
3. Volume of transfusion
    a. Children: Transfuse 4 ml/kg per gram increase in hemoglobin desired. The calculation uses post-transfusion hemoglobin of 13 g/dl on 3-week and 14 g/dl on 4-week schedule
    b. Adults: 2, 3 or 4 units per transfusion. Generally: 3 units if pre-transfusion hemoglobin
4. Other volume considerations

a. Patients with intact spleen have higher transfusion needs; Splenectomy is not recommended unless under exceptional circumstances
b. Adults with body weight > 60 kg may need 4 units on some transfusions
c. Higher hemoglobin target or transfusion more frequent than every 3 weeks are needed in rare circumstances
    i. Congestive heart failure
    ii. Pulmonary hypertension
    iii. Symptomatic extramedullary hematopoietic masses
    iv. Occurrence of fatigue or bone pain in pre-transfusion period

5. Rate of transfusion
    a. Children: 5 ml/kg/h
    b. Adults: 200–300 ml/h, based on tolerance
    c. Congestive heart failure: Reduce volume and rate based on cardiac function

Decline of splenectomy in thalassemia

The gradual decline of splenectomy in thalassemia major has had a significant impact on transfusion management. An association between higher pre-transfusion hemoglobin levels and decrease in the rate of splenectomy has been documented. This supports the clinical observation that development of splenomegaly in thalassemia is the consequence of maintaining low hemoglobin levels. Aiming for lower pre-transfusion hemoglobin can be counterproductive as it promotes splenic enlargement with a secondary rise in transfusion needs. Caution is needed when referring to older transfusion guidelines developed in an era when most adults with thalassemia were splenectomized.

Iron chelation therapy

Transfusional iron overload is the most important complication of red cell transfusions in thalassemia, and the iron loading rate affects the efficacy of chelation therapy. Until the availability of oral agents, the only available iron chelator was **deferoxamine**, which was difficult to use and had significant toxicity in young children. These concerns about iron overload influenced the development of guidelines for transfusion therapy. The management of iron overload has been transformed with the availability of oral chelators **deferasirox** and **deferiprone**, and the development of novel chelation regimens. In current practice, transfusion volume and frequency should be selected based on the need to correct anemia and suppress marrow hyperplasia. A suitable chelation regimen can then be devised to maintain iron overload in the safe range.

Other recommendations

- Thalassemia is a rare disease in the U.S. where the expertise for management is concentrated in specialty centers in a few large metropolitan areas.
- It is recommended that transfusion therapy should be directly supervised by a hematologist with expertise in thalassemia. Where this is not possible due to the distance from a specialty center, the transfusion plan should be devised and periodically reviewed by a hematologist with expertise in thalassemia.
- Options for stem cell transplant should be discussed soon after the diagnosis is confirmed and disease modifying therapies should be offered where appropriate.
- It is necessary to develop thalassemia-specific protocols for patients receiving regular RBC transfusions to ensure optimal long-term outcomes. The indication for use of RBC units should be clearly identified as thalassemia for proper communication between ordering physician and blood bank.
- An accurate record of transfusion volume at each visit must be maintained, which can be then used to calculate annual transfusion requirement and iron loading rate.
- Development of iron overload should be evaluated with serial ferritin measurements after the first 6 months of transfusions. When patients are transfused at multiple facilities, antibody history must be obtained from other hospitals and documented in patient's record.

1.3 European Guidelines

The most recent European recommendations for the management of beta thalassemia were published in the European Medical Journal in 2017[7]. They consist of a summary of scientific sessions on β-thalassemia that took place on 2nd–4th February 2017, as part of the European Hematology Association Scientific Working Group meeting. No specified grade of evidence or level of recommendation were provided. The below recommendations were made:

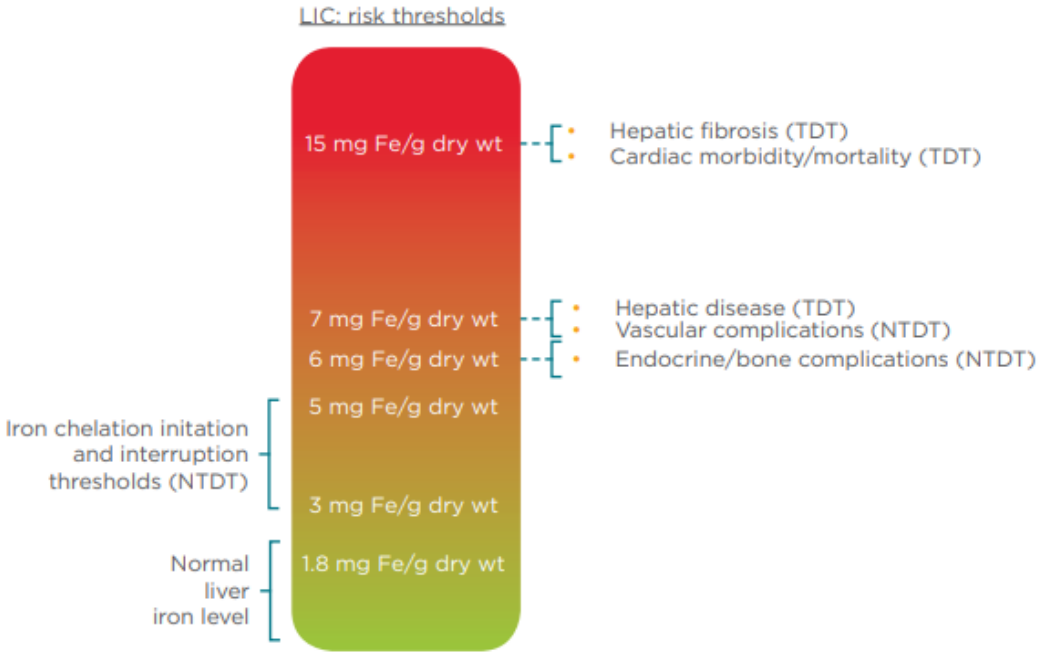
Iron Homeostasis in β-Thalassemias

The conventional treatment of severe β-thalassemias is regular blood transfusion, which is associated with iron overloading and results in multiple extrahepatic morbidities. To prevent organ complications due to iron overload the patient must be chelated, as the human body has many mechanisms for absorbing, transferring, and storing iron, but none for its excretion.

The most common test for iron overload is serum ferritin; however, liver iron concentration remains a gold standard, as the liver is the primary site for iron

storage (> 70% of body iron) and correlates with the total body iron. Given that liver iron concentrations ≥ 5 mg/kg have been linked to an increased prevalence of vascular, endocrine, and bone morbidities, the latest Thalassemia International Federation (TIF) guidelines advise that, as a minimum, serum ferritin should be tested every 3 months, magnetic resonance imaging (MRI) to measure iron liver concentration should be measured every year and T2* MRI of the heart should be undertaken every 1–2 years, according to the patient's iron status.

As β-thalassemia is most prevalent in developing countries, recommendations for iron monitoring must also consider the availability of resources. To allow for scenarios where MRI facilities are unavailable, a clinical scale indicating the complications associated with liver iron concentration, measured by MRI or liver biopsy, has been developed (**Figure 1**).



LIC: liver iron concentration; NTDT: non-transfusion-dependent thalassemia; TDT: transfusion-dependent thalassemia; wt: weight.

***Figure 1**. Liver iron concentration thresholds and their clinical implications in non-transfusion-dependent thalassemia. Retrieved from EHA 2017 recommendations.*

Iron chelation therapy aims to maintain safe levels of body iron by balancing iron intake with iron excretion, to remove excess stored iron that has accumulated after blood transfusions, or in emergencies as an intense treatment to remove excess iron quickly to reverse the effects of heart failure.

Iron chelation therapy for thalassemia patients is evolving; in the 1970s regular transfusion was normal practice, which progressed to chelating agents in the 1980s

with the introduction of **deferoxamine** (DFO). In 1999, the T2* MRI technique was introduced in the UK, and in the same year **deferiprone** (DFP) was approved in Europe, followed by approval of **deferasirox** (DFX) in 2006; both are oral drugs whereas DFO is administered by subcutaneous infusion.

Parallel to these advances in chelation therapy, a reduction in mortality was observed from 12.7 deaths per 1,000 patient years from 1980–1999, to 4.3 deaths per 1,000 patient years from 2000–2003. Use of DFO has reduced significantly since the introduction of the oral iron chelators DFP and DFX; however, the use of subcutaneous/intravenous DFO is still utilized for patients with heart failure or when a quick reduction of elevated serum ferritin is required (7,000–10,000 ng/mL).

Combination therapy of DFO and DFP can also enhance myocardial iron removal in TDT patients with myocardial overload.

DFX provides significant improvement in iron overload according to myocardial T2* MRI over a 3-year period in patients with TDT, and liver iron concentration and serum ferritin were halved in severely iron-overloaded patients over the same time period.

These improvements are accompanied by an improvement of liver pathology status in patients with β-thalassemia.

Novel Therapies

New treatments for β-thalassemia can also target ineffective erythropoiesis through pharmacological intervention, such as disruption of the JAK2/STAT5 pathway with the JAK2 inhibitor, ruxolitinib. High levels of EPO lead to hyperactivation of phospho-JAK2, which expands immature red cell precursors unable to mature and reduce red blood cell production. Ruxolitinib is a potent and selective oral JAK1 and JAK2 inhibitor, approved for use in myelofibrosis and polycythemia vera. Ruxolitinib is associated with a clinically relevant improvement in splenomegaly in these disorders. The efficacy and safety of ruxolitinib was tested in a Phase IIa trial of regularly transfused β-thalassemia patients. The primary endpoint was the reduction of transfusion requirement and the secondary endpoints included reduction of spleen volume. Clinically meaningful reductions in mean spleen volume were observed, suggesting that ruxolitinib might serve as an alternative option in patients with TDT who are potential candidates for splenectomy.

1.4 International Guidelines

1.4.1 Thalassemia International Federation (TIF) Management of Transfusion-Dependent Thalassemia [2022]

The most recent international guidelines for the management of transfusion-dependent beta-thalassemia were summarized and published in 2022[8]. The below recommendations were made:

I. Blood transfusion

The aim of blood transfusion in thalassemia is to deliver a safe and effective transfusion regimen whilst minimizing the burden of transfusion therapy on everyday life.

An effective transfusion regimen will result in:

- Good growth and development
- Good energy levels
- Sufficient suppression of intra and extramedullary hematopoiesis.

A safe transfusion regimen will:

- Use a product that is collected, tested, selected, issued, and administered adherent to established quality and safety regulations and guidance.
- Be administered by staff trained in blood transfusion.
- Involve informed patient consent.
- Be performed in a system with a good hemovigilance structure.

Criteria for initiating transfusion therapy

For deciding whom to transfuse, the following should be included in the investigations:

- Confirmed diagnosis of thalassemia
- Laboratory criteria:
    - Hemoglobin level (Hb) 2 weeks apart (excluding all other contributory causes such as infections) AND/OR
- Clinical criteria irrespective of hemoglobin level:
    - Hemoglobin > 70 g/l with any of the following:
        - Significant symptoms of anemia

- Poor growth / failure to thrive
- Complications from excessive intramedullary hematopoiesis such as pathological fractures and facial changes
- Clinically significant extramedullary hematopoiesis

Recommendations

- Confirm the diagnosis of thalassemia and appropriate clinical and laboratory for transfusion (IIA).
- Blood transfusion requires informed consent.
- Hemovigilance and adverse events reporting are key to the safety of blood transfusion.
- Use careful donor selection and screening, favoring voluntary, regular, non-remunerated blood donors (IIA).
- Before first transfusion, perform extended red cell antigen typing of patients at least for D, C, c, E, e and Kell (IIA) and if available a full red cell pheno/genotype. 4At each transfusion, give ABO, Rh(D) compatible blood. Choosing units compatible for ABO, C, c, E, e and Kell antigens is highly recommended (IIA).
- Before each transfusion, perform a screen for new antibodies and an IAT crossmatch, or in centers that meet regulatory requirements, perform an electronic crossmatch where allowed (IA).
- Use leucodepleted packed red cells where available. Pre-storage filtration is strongly recommended, but blood bank pre-transfusion filtration is acceptable. Bedside filtration is only acceptable if there is no capacity for pre-storage filtration or blood bank pre-transfusion filtration (IA).
- Use washed red cells for patients who have severe allergic reactions (IIA).
- Transfuse red cells stored in CPD-A within one week of collection and red cells stored in additive solutions within two weeks of collection where available. (IA).
- Transfuse every 2-5 weeks, maintaining pre-transfusion hemoglobin above 95-105 g/l or up to 110-120 g/l for patients with cardiac complications (IA).
- Keep a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient (IIA).
- Keep the post-transfusion hemoglobin below 130-150 g/l (IIA).

II. Iron overload

Iron overload occurs when iron intake is increased over a sustained period of time, either as a result of red blood cell transfusions or increased absorption of iron through the gastrointestinal (GI) tract. Both of these occur in thalassemias, with blood transfusion therapy being the major cause of iron overload in thalassemia major and increased GI absorption being more important in non-transfusion dependent thalassemia (NTDT). When thalassemia major patients receive regular blood transfusion, iron overload is inevitable because the human body lacks a mechanism to excrete excess iron. Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities.

Diagnosis and monitoring of iron overload

The diagnosis and monitoring of iron overload are based on the complementary use of the following parameters:

a. Serum ferritin (SF)

SF concentration is measured at least every 3 months (1-3 months). Target value is currently between 500-1000 µg/l. Measuring the trends in SF over a period of at least 3 months is a more reliable indicator for adjusting therapy than the use of single values. When ferritin is > 4000 µg/l, it is much harder to see a trend in ferritin. It is recognized that SF may not reflect total body iron levels or organ-specific levels in some patients. SF needs to be interpreted together with liver iron concentration (LIC) and myocardial iron since it fluctuates in response to inflammation, abnormal liver function and metabolic deficiencies.

b. Liver iron concentration (LIC)

LIC is measured by magnetic resonance imaging (MRI)-based methods. LIC of 3-7 mg/g dry weight (dw) is an acceptable therapeutic goal in TM patients. It is recommended that levels are kept towards the lower part of this range. The frequency of LIC assessment should be guided by its level and its rate of change: e.g:

- Stable levels in the range 3-7 mg/g dw: Every one or two years
- Levels >7 mg/g dw: yearly or more often
- Levels falling rapidly 6-12 monthly

c. Myocardial iron

Myocardial iron is assessed by T2* cardiac MRI, using an externally validated protocol and software which should undergo at least annual external calibration and other measurements to ensure validation of the measurement process.

The frequency of cardiac MRI scan should be guided by myocardial iron level, for example:

- Stable T2* >20 milliseconds: two yearly
- T2* 10-19 milliseconds: yearly
- T2* < 10 milliseconds: 6months

It is particularly important to measure left ventricular function when cardiac iron is high (e.g. T2*< 10ms) as this is associated with a high risk of deteriorating function which requires urgent intensification of chelation.

LIC and myocardial iron should be monitored regularly in patients from age 9 or younger if they are able to tolerate MRI scanning without sedation.

Recommendations

- Uncontrolled transfusional iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis and hepatocellular carcinoma (B).
- Liver iron concentration can be used to calculate total body iron, and serum ferritin is an approximate marker of LIC (B).

III. Iron chelation

Aims of iron chelation therapy

- Preventive therapy: to maintain safe levels of body iron at all times, by balancing iron intake from blood transfusion with iron excretion by chelation (iron balance).
- Rescue therapy: to remove excess iron stored in the body.
- Emergency therapy: to urgently intensify iron chelation in case of iron-induced heart failure.
- Dose adjustment of therapy: to adjust dosing and treatment regimens to changing circumstances identified by careful monitoring of body iron and its distribution; monitoring is important to avoid:
    - under-chelation with increased iron toxicity; or
    - over-chelation and increased chelator toxicity.

Adherence to therapy: to adhere to prescribed regular regimen; intermittent high-dose chelation can induce negative iron balance but does not provide continuous protection from labile iron and risks increased toxicity from the iron chelator.

Iron chelators: Three iron chelators are currently licensed for clinical use; their properties and indicated doses are reviewed in **table 9.**

Table 9. Licensed Indications for Chelation in Thalassemia

Category	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
A. Children aged 2-6 years	First line for thalassemia major (TM)	Under European licensing, there is limited data available on the use of deferiprone in children. Under USA licensing, deferiprone oral solution is an iron chelator indicated for the treatment of transfusional iron overload in adult and pediatric patients 3 years of age and older with thalassemia syndromes, sickle cell disease and other anemias.	First line in USA Under European licensing DFX is used when DFO is contraindicated or inadequate
B. Children aged > 6 years and adults	First line for TM	Under European licensing DFP Deferiprone is approved if other chelators or DFO is not tolerated or inadequate. Under USA licensing, DFP tablets are an iron chelator indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with thalassemia syndromes, sickle cell disease and other	First line TM First line NTDT

		anemias For ages below 8 years and over 3 years oral solution can be used.	
Route	SC/IM or IV	Oral, tablet, or liquid	Oral, dispersed tablet
Dosage and frequency	20-60 mg/kg 5-7 d/week, 50 mg/kg in EU Children's dose up to 40 mg/kg	75-100 mg/kg/day in 3 divided doses daily 75-99 mg/kg/d Oral Twice-A-Day (TAD) Formulation Ferriprox® (FDA approved)	14-28 mg/kg/day once daily for film coated tablet. Lower doses in NTDT.
Contraindications	Pregnancy (but has been used in 3rd trimester) Hypersensitivity	Pregnancy History of neutropenia or condition with underlying risk of cytopenia Hypersensitivity including Henoch Schönlein purpura: urticaria and periorbital oedema with skin rash	Pregnancy Hypersensitivity Estimated creatinine clearance < 60 mL/min Hepatic impairment or renal failure
Precautions	Monitor ferritin; if it falls to < 1000 µg/L, reduce dose (so mean daily dose/ferritin remains < 0.025). Monitor audiometry regularly, particularly as ferritin falls. Monitor eyes regularly including electroretinography if on high doses. Fever suggestive of septicemia with organisms	Measure neutrophil count (ANC) before starting and monitor ANC weekly. Under European licensing, the patient's ANC should be monitored every week during the first year of therapy. For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the	Monitor creatinine trends for 1st 4 weeks after starting or after dose escalation, then monthly. If rapid fall in serum ferritin to < 1000 µg/L, dose reduce. If ferritin 500 µg/L consider very low doses. Proteinuria may occur occasionally with renal

	that used ferrioxamine (Yersinia, Klebsiella). Renal failure or diminishing renal function with other comorbidities.	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 deferiprone therapy. In the USA licensing, the below is mentioned: • Due to the risk of agranulocytosis, monitor ANC before and during FERRIPROX therapy. Test ANC prior to start of FERRIPROX therapy and monitor on the following schedule during treatment: First six months of therapy: Monitor ANC weekly; • Next six months of therapy: Monitor ANC once every two weeks; • After one year of therapy: Monitor ANC every two to four weeks (or at the patient's blood transfusion interval in patients. For neutropenia (ANC < 1.5 x 10^9/L), interrupt treatment.	tubular acidosis. Monitor urine protein regularly. Prescribing to the elderly; non-fatal gastrointestinal bleeding, ulceration, and irritation may occur; caution with drugs of known ulcerogenic or hemorrhagic potential, (e.g. NSAIDs, corticosteroids, oral bisphosphonates, and anticoagulants). Hypersensitivity reactions. Monitor liver function regularly.

		For agranulocytosis (ANC < 0.5 x 10^9/L), consider hospitalization. Advise patients to report immediately symptoms of infection; interrupt if fever develops. Monitor for symptoms of arthropathy. Monitor liver function regularly. No guidance on dose adjustment at low ferritin.	
Potential drug interactions	Co-administration with prochlorperazine: may lead to temporary impairment of consciousness. Gallium-67: Imaging results may be distorted by rapid urinary excretion of deferoxamine-bound gallium-67. Discontinuation 48 hours prior to scintigraphy is advisable.	Theoretical interactions with UGT1A6 inhibitors (e.g. diclofenac, probenecid or silymarin (milk thistle). Avoid concomitant use with drugs associated with neutropenia. Gallium-67 as with DFO. Oral preparations containing polyvalent cations (e.g., aluminum containing antacids and zinc) allow at least a 4-hour interval.	Theoretical interactions with drugs metabolized by CYP3A4 e.g. midazolam. Theoretical interactions with drugs metabolized by CYP1A2: e.g. theophylline. Gallium-67 as with DFO. Oral preparations containing polyvalent cations as with DFP.

Recommendations

- Chelation therapy is an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-induced iron overload (A).
- Chelation therapy at the correct doses and frequency can balance iron excretion with iron accumulation from transfusion (A).
- Absolute change in total body iron in response to chelation can be calculated from change in LIC (B).
- Direction of change in body iron in response to transfusion and chelation can usually but not always be estimated from the trend in serum ferritin (B).
- Prevention of iron accumulation using chelation therapy is preferable to rescue treatment because iron-mediated damage is often irreversible, and removal of storage iron by chelation is slow - particularly after it has escaped the liver (B).
- Response to chelation is dependent on the dose applied and the duration of exposure (A).
- Response to chelation is affected by the rate of blood transfusion (B).
- Cardiac iron accumulates later than liver iron, and is rare before the age of 8 years, affecting a subset of patients (B).
- The chelation of storage iron from the liver tends to be faster than from myocardium (B).
- Cardiac storage iron concentration is directly related to the risk of heart failure, which can be reliably estimated by MRI (e.g. cardiac T2*), provided the center performing the measurement uses a validated method that has been independently calibrated (B).
- Chelation can reverse iron-mediated cardiac dysfunction rapidly (within weeks) by rapid chelation of labile iron, if 24 h chelation cover is achieved (A).
- Chelation therapy removes myocardial storage iron slowly (months or years) (A).
- Over-chelation increases side effects from chelation therapy, and doses should therefore be decreased as serum ferritin or liver iron levels fall (demonstrated most clearly with DFO) (B).
- The optimal chelation regime must be tailored for the individual and will vary with their current clinical situation.

- Chelation therapy will not be effective if it is not taken regularly – a key aspect of chelation management is to work with patients to optimize adherence (B).

IV. Hematopoietic stem cell transplantation (HSCT)

- HSCT should be offered at an early age, before complications due to iron overload have developed, if an HLA identical sibling is available.
- Either bone marrow or cord blood from an HLA-identical sibling can be used.
- A matched unrelated donor can be used, provided that high compatibility criteria for both HLA class I and II loci are present.
- Haploidentical HSCT in thalassemia can be considered in experienced HSCT centers in the context of well-designed clinical trials.
- Myeloablative conditioning regimens should always be used for standard transplantation.
- Post-transplant care should include all transplant- and thalassemia-related complications.
- In thalassemia patients, HSCT is cost-effective when compared to life-long supportive therapy.

V. Hematopoietic stem cell (HSC) transplantation or gene therapy

While waiting for the long–term clinical data on gene therapy for β–thalassemia, currently and on the basis of existing indications, patients with β–thalassemia major have potentially the following options for treatment:

- Allogeneic hematopoietic stem cell (HSC) transplantation: young patients (≤17 years old) with a β+ or β0 genotype having an HLA-compatible sibling or a 10/10 matched volunteer donor.
- Gene therapy with betibeglogene autotemcel: young patients in the 12- to 17-year-old age group with a β+ genotype who do not have an HLA-compatible sibling donor.
- Gene therapy with betibeglogene autotemcel: patients in the 17- to 55-year-old age group with a β+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo an allo-HSC transplant but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

VI. Novel therapies

- Luspatercept can be considered for:
    - Patients who require regular red blood cell transfusions,

    - ≥ 18 years of age.
- The recommended starting dose of luspatercept is 1 mg/kg once every 3 weeks by subcutaneous injection.
- If the pre-dose hemoglobin level is ≥115 g/l and is not influenced by recent transfusion, consider delaying dosing of luspatercept until the level is ≤110 g/l.
- Before administration of luspatercept, hemoglobin level and liver function tests including alanine transferase and aspartate transferase levels should be monitored to ensure proper dosing and metabolism of the medication.
- If a TDT patient does not achieve a reduction in red cell transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the luspatercept dose to 1.25 mg.
- If a patient experienced a response followed by a lack of or lost response to luspatercept, consider initiating a search for causative factors.
- Luspatercept should be discontinued if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.
- As thromboembolic events were reported in 8/223 (3.6%) of luspatercept-treated patients, it is important to monitor any TDT patient receiving luspatercept for signs and symptoms of thromboembolic events and initiate treatment accordingly.
- Hypertension was reported in 10.7% (61/571) of luspatercept-treated patients. It is therefore recommended that blood pressure be monitored prior to each administration.
- Luspatercept may cause fetal harm. While no data are currently available on its use in pregnant women, all pregnant women should be advised of the potential risk to a fetus.
- Safety and efficacy of luspatercept in pediatric patients has not yet been established. Its use in pediatric patients is therefore not currently recommended.

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses on the management of Thalassemia.

Table 10. Systematic Reviews and Meta-Analyses for the Management of Thalassemia

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Soliman et al[9]. (2022)	**Efficacy and safety of calcium channel blockers in preventing cardiac siderosis in thalassemia patients: An updated meta-analysis with trial sequential analysis**	Establish evidence regarding the effect of amlodipine on cardiac iron overload in thalassemia patients.	The primary outcomes were cardiac T2* and myocardial iron concentration (MIC). Secondary outcomes were liver iron concentration (LIC), risk of Gastrointestinal (G.I.) upset and risk of lower limb edema. We used Hedges' *g* to pool continuous outcomes, while odds ratio was used for dichotomous outcomes.	Amlodipine had a statistically significant lower MIC (Hedges' $g = -0.82$, 95% confidence interval [CI] [−1.40, −0.24], $p < .001$) and higher cardiac T2* (Hedges' $g = 0.36$, 95% CI [0.10, 0.62], $p = .03$). Amlodipine was comparable to standard chelation therapy in terms of the risk of lower limb edema and GI upset.
2	Hatamleh et al. (2023)[10]	**Efficacy of Hydroxyurea in Transfusion-Dependent Major β-Thalassemia Patients: A Meta-Analysis**	Evaluate the efficacy of hydroxyurea in patients with transfusion-dependent B-thalassemia.	Outcomes assessed in the present meta-analysis included transfusion in one year and intervals between transfusions (in days). Other outcomes assessed were fetal hemoglobin (%),	The mean interval between transfusions was significantly higher in patients receiving hydroxyurea compared to those not receiving hydroxyurea (mean deviation {MD}: 10.07, 95% CI: 2.16, 17.99). Hemoglobin was significantly higher in

				hemoglobin (%), and ferritin levels (ng/dl).	patients receiving hydroxyurea compared to its counterparts (MD: 1.71, 95% CI: 0.84, 2.57). Patients receiving hydroxyurea had significantly lower ferritin levels compared to those not receiving hydroxyurea (MD: -299.65, 95% CI: -518.35, -80.96). These findings suggest that hydroxyurea may be a promising and cost-effective alternative to blood transfusions and iron chelation therapies for beta-thalassemia patients. However, further RCTs are needed to validate these findings and to determine the optimal dosages and treatment regimens for hydroxyurea in this patient population.

Section 2.0 Drug Therapy

2.1 Iron-Chelating agents

2.1.1 Deferoxamine

Information on deferoxamine is detailed in the table below[11,12]:

Table 11. Deferoxamine Drug Information

SCIENTIFIC NAME DEFEROXAMINE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	DESFERAL, FROXA
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D56
Drug Class	CHELATOR
Drug Sub-class	IRON-CHELATING AGENTS
ATC Code	V03AC01
Pharmacological Class (ASHP)	IRON-CHELATING AGENTS
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection/infusion Powder for injection
Route of Administration	Intravenous use Subcutaneous use
Dose (Adult) [DDD]*	**IM**: 500 mg to 1 g/day (maximum: 1 g/day). **IV**: 40 to 50 mg/kg/day (maximum: 60 mg/kg/day) over 8 to 12 hours for 5 to 7 days per week. **SUBQ**: 1 to 2 g/day or 20 to 40 mg/kg/day (maximum: 60 mg/kg/day) over 8 to 24 hours for 5 to 7 days per week.

Maximum Daily Dose Adults*	**IM**: maximum: 1 g/day. **IV**: maximum: 60 mg/kg/day. **SUBQ**: maximum: 60 mg/kg/day.
Dose (pediatrics)	Children and Growing Adolescents: SUBQ infusion: 20 to 40 mg/kg/day over 8 to 12 hours, 6 to 7 nights per week, maximum daily dose: 40 mg/kg/**day**. Adolescents once growth has ceased: SUBQ infusion (preferred): 40 to 60 mg/kg/day over 8 to 12 hours, 6 to 7 nights per week, maximum daily dose: 2,000 mg/**day**. SUBQ bolus: 45 mg/kg/dose, 5 times per week.
Maximum Daily Dose Pediatrics*	Children and Growing Adolescents: SUBQ infusion: 40 mg/kg/**day**. Adolescents once growth has ceased: SUBQ infusion (preferred):2,000 mg/**day**.
Adjustment	**Altered Kidney Function:** • CrCl >50 mL/minute: No adjustment required • CrCl 10 to 50 mL/minute, CRRT: Administer 25% to 50% of normal dose • CrCl<10 mL/minute, hemodialysis, peritoneal dialysis: Avoid use **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, PA
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a physician specialized in the management of thalassemia (e.g. hematologist).
PA (Prior Authorization)[13]	Must meet all:

	1-Diagnosis of chronic iron overload due to transfusion-dependent anemia (e.g., congenital/acquired anemias including thalassemia, sickle cell anemia, aplastic anemia, myelodysplasia); 2-Transfusion history of ≥ 100 mL/kg of packed red blood cells (e.g., ≥ 20 units of packed red blood cells for a 40 kg person) and a serum ferritin level > 1,000 mcg/L; 3-Dose does not exceed any of the following (a, b or c): a. SC: 2,000 mg per day; b. IV: 40 mg/kg per day for children; 60 mg/kg per day for adults; c. IM: 1,000 mg per day. Approval duration: 6 months
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** hypotension, tachycardia, abdominal pain, diarrhea, nausea, vomiting. **Most serious**: leukopenia, thrombocytopenia, anaphylaxis (including anaphylactic shock), angioedema.
Drug Interactions*	**Category X:** Betibeglogene Autotemcel.
Special Population	N/A
Pregnancy	Adverse events have been observed in animal reproduction studies. Toxic amounts of iron or deferoxamine have not been noted to cross the placenta; however, the metabolic effects of a maternal overdose may adversely affect the fetus. In case of acute iron toxicity,

	treatment during pregnancy should not be withheld.
Lactation	It is not known if deferoxamine is present in breast milk. One patient who received deferoxamine during lactation for beta thalassemia exhibited normal breast milk iron concentrations. Adverse events were not reported in her breastfed twins. The manufacturer recommends that caution be exercised when administering to breastfeeding women.
Contraindications	Hypersensitivity to deferoxamine or any component of the formulation; patients with severe renal disease or anuria.
Monitoring Requirements	Serum iron, ferritin, total iron-binding capacity, CBC with differential, renal function tests (serum creatinine), liver function tests, serum chemistries; ophthalmologic exam (visual acuity tests, fundoscopy, slit-lamp exam) and audiometry with long-term treatment; growth and body weight in children (every 3 months). When deferoxamine complexes with iron it forms a water-soluble compound (ferrixoamine) that imparts discoloration of the urine; often described as vin rosé (dark pink) discoloration to the urine.
Precautions	***Concerns related to adverse effects:*** **Acute respiratory distress syndrome (ARDS):** Deferoxamine has been associated with ARDS following excessively high-dose IV treatment of acute iron intoxication or thalassemia; has been reported in children and adults. **Auditory effects:** Auditory disturbances (tinnitus and high frequency hearing loss) have been reported following prolonged administration, at high

	doses, or in patients with low ferritin levels; effects are generally reversible with early detection and immediate discontinuation. Elderly patients are at increased risk for hearing loss. Audiology exams are recommended with long-term treatment. **Growth retardation:** High deferoxamine doses and concurrent low ferritin levels are also associated with growth retardation. Growth velocity may partially resume to pretreatment rates after deferoxamine dose reduction. **Infection:** Patients with iron overload are at increased susceptibility to infection with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis;* treatment with deferoxamine may enhance this risk; if infection develops, discontinue therapy until resolved. **Infusion reactions:** Flushing of the skin, hypotension, urticaria, and shock are associated with rapid IV infusion; administer by slow IV infusion, IM, or slow subcutaneous infusion only. **Mucormycosis:** Rare and serious cases of mucormycosis (including fatalities) have been reported with use; withhold treatment with signs and symptoms of mucormycosis. **Ocular effects:** Ocular disturbances (blurred vision; cataracts; corneal opacities; decreased visual acuity; impaired peripheral, color, and night vision; optic neuritis; retinal pigment abnormalities; retinopathy; scotoma; visual loss/defect) have been reported following prolonged administration, at high doses, or in patients with low ferritin levels; effects are generally

	reversible with early detection and immediate discontinuation. Elderly patients are at increased risk for ocular disorders. Periodic ophthalmic exams are recommended with long-term treatment. **Renal effects:** Increases in serum creatinine, acute renal failure and renal tubular disorders have been reported; monitor for changes in renal function. Deferoxamine is readily dialyzable. When iron is chelated with deferoxamine, the chelate is water-soluble and is excreted renally. **Urine discoloration:** Patients should be informed that urine may have a pink, reddish, or orange discoloration (often referred to as *vin rosé* discoloration). ***Concurrent drug therapy issues:*** **Ascorbic acid**: Combination treatment with ascorbic acid (>500 mg/day in adults) and deferoxamine may impair cardiac function (rare), effects are reversible upon discontinuation of ascorbic acid. If combination treatment is warranted, initiate ascorbic acid only after one month of regular deferoxamine treatment, do not exceed ascorbic acid dose of 200 mg/day for adults (in divided doses), 100 mg/day for children ≥10 years of age, or 50 mg/day in children <10 years of age; monitor cardiac function. Do not administer deferoxamine in combination with ascorbic acid in patients with preexisting cardiac failure.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of thalassemia treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Deferoxamine

Deferoxamine is recommended as a first-line treatment for iron overload in patients with thalassemia. It is given as 500 mg to 1 g/day (IM), 40 to 50 mg/kg/day (IV) over 8 to 12 hours for 5 to 7 days per week.

2.1.2 Deferiprone

Information on deferiprone is detailed in the table below[14,15]:

Table 12. Deferiprone Drug Information

SCIENTIFIC NAME DEFERIPRONE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	FERRIPROX
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D56
Drug Class	CHELATOR
Drug Sub-class	IRON-CHELATING AGENTS
ATC Code	V03AC02
Pharmacological Class (ASHP)	IRON-CHELATING AGENTS
DRUG INFORMATION	
Dosage Form	Film-coated tablet Oral solution
Route of Administration	Oral use
Dose (Adult) [DDD]*	Initial: 75 mg/kg/day in 2 divided doses (using 1,000 mg twice-a-day tablet formulation only) or in 3 divided doses

	(using oral solution, 500 mg tablet, or 1,000 mg 3-times-a-day tablet formulation); individualize dose based on response and therapeutic goal. Dosing may start at 45 mg/kg/day and be increased weekly by 15 mg/kg/day increments until 75 mg/kg/day is achieved to minimize GI upset.
Maximum Daily Dose Adults*	99 mg/kg/day
Dose (pediatrics)	***Initial dosing***: Children <8 years: Limited data available in ages <3 years: Oral solution: Oral: 25 mg/kg/dose 3 times daily; round dose to the nearest 250 mg (2.5 mL); may consider a lower dose of 15 mg/kg/dose 3 times a day titrated in 15 mg/kg increments at weekly intervals to minimize GI side effects when initiating therapy. Children ≥8 years and Adolescents: *Three-times-daily dosing:* Oral solution, 3-times-daily 500 mg or 1,000 mg tablet formulations: Oral: Initial: 25 mg/kg/dose 3 times daily; for oral solution, round dose to the nearest 250 mg (2.5 mL); for tablets, round dose to the nearest $^1/_2$ tablet; may consider a lower initial dose of 15 mg/kg/dose 3 times a day titrated in 15 mg/kg increments at weekly intervals to minimize GI side effects when initiating therapy. *Two-times-daily dosing:* Twice-daily 1,000 mg tablet formulation: Oral: Initial: 37.5 mg/kg/dose every 12 hours; round dose to the nearest 500 mg; may consider a lower dose of 22.5 mg/kg/dose every 12 hours titrated in 15 mg/kg increments at weekly intervals to minimize GI side effects when initiating therapy.

	Maintenance dosing: Children and Adolescents: Monitor serum ferritin every 2 to 3 months with therapy per the manufacturer; individualize dose based on response and therapeutic goals for hemoglobinopathy; not to exceed maximum daily dose: 99 to 100 mg/kg/**day**. If serum ferritin falls consistently below 500 mcg/L, consider temporary treatment interruption until serum ferritin rises above 500 mcg/L.
Maximum Daily Dose Pediatrics*	99 mg/kg/day
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a physician specialized in the management of thalassemia (e.g. hematologist).
PA (Prior Authorization)[13]	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache, abdominal pain, fever, nausea, vomiting. **Most serious**: cardiac failure, pulmonary embolism, pancreatitis, anaphylactic shock.
Drug Interactions*	**Category X:**

	Alcohol (ethyl), Betibeglogene Autotemcel, UGT1A6 Inhibitors.
Special Population	N/A
Pregnancy	Based on data from animal reproduction studies, in utero exposure to deferiprone may cause fetal harm. Outcome information following deferiprone use in pregnancy is limited. Deferiprone should be discontinued if pregnancy occurs. When iron chelation therapy is needed in a pregnant woman, agents other than deferiprone are preferred.
Lactation	It is not known if deferiprone is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends that women avoid breastfeeding during deferiprone treatment and for 2 weeks after the last dose.
Contraindications	Hypersensitivity to deferiprone or any component of the formulation Severe neutropenia (ANC <500/mm^3) Pregnancy Breastfeeding.
Monitoring Requirements	Serum ferritin (every 2 to 3 months); ANC (at baseline, weekly during the first 6 months of therapy, every 2 weeks for the next 6 months of therapy, and then every 2 to 4 weeks [or at the patient's blood transfusion interval if an interruption due to any ANC decrease has not occurred] thereafter; reduction in ANC monitoring may be considered on an individual basis); if ANC <1,500/mm^3, monitor CBC, WBC (corrected for nucleated RBCs), ANC, and platelets daily until ANC recovery; ALT (at baseline and monthly); zinc

	levels (at baseline and regularly); signs or symptoms of infection; pregnancy status (prior to initiation and as clinically indicated).
Precautions	***Concerns related to adverse effects:*** **Agranulocytosis/Neutropenia:** May cause agranulocytosis, which could lead to serious infections (some fatal) and may be preceded by neutropenia. If ANC <500/mm^3, consider hospitalization (and other clinically appropriate management); do not resume or rechallenge unless the potential benefits outweigh potential risks. Neutropenia and agranulocytosis were generally reversible upon discontinuation. The mechanism for deferiprone-induced agranulocytosis is not known. Avoid concurrent use with other agents associated with neutropenia (or agranulocytosis). **Hepatotoxicity:** Elevations in ALT values have been observed; consider treatment interruption for persistent ALT elevations. **Hypersensitivity:** Hypersensitivity reactions have been reported, urticaria, and periorbital edema with skin rash. **Zinc deficiency:** Lower plasma zinc concentrations have been observed; supplementation may be needed**.**
Black Box Warning	**Agranulocytosis/neutropenia:** Deferiprone can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. Measure the ANC before starting deferiprone therapy and monitor regularly while on therapy.

	Interrupt deferiprone therapy if neutropenia develops. Interrupt deferiprone therapy if infection develops and monitor the ANC more frequently. Advise patients taking deferiprone to report immediately any symptoms indicative of infection.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of thalassemia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for deferiprone.**

Table 13. Deferiprone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Deferiprone	NICE	N/A
	CADTH[16]	March 2016: The Canadian Drug Expert Committee (CDEC) recommends that deferiprone be listed for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate, if the following condition is met: *Condition*: List in a manner similar to deferasirox. At the submitted price, the annual cost of treatment with deferiprone ($49,866 to $66,488 for a 60 kg patient) is similar to treatment with deferasirox ($37,165 to $74,329 for a 60 kg patient).
	HAS[17]	July 2018: The laboratory does not request reimbursement for monotherapy in the treatment of iron overload in patients with thalassemia major when current chelation treatment with deferasirox is contraindicated or unsuitable.

		October 2018: High clinical benefit combined with deferoxamine (DESFERAL) in thalassemia major, when monotherapy with a different iron chelator is ineffective, or when iron overload is life-threatening, and minor clinical added value compared to deferoxamine monotherapy. Insufficient clinical benefit combined with deferasirox (EXJADE) to justify its reimbursement for this same indication.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Deferiprone

Deferiprone is recommended as a first-line treatment for iron overload in patients with thalassemia. It is given as 75 mg/kg/day in 2 divided doses or in 3 divided doses. Its use is backed up by several HTA bodies namely CADTH. However, HAS rejected its reimbursement as monotherapy, and concluded that actual clinical benefit is high when combined with deferoxamine.

2.1.3 Deferasirox

Information on deferasirox is detailed in the table below[18,19]:

Table 14. Deferasirox Drug Information

SCIENTIFIC NAME DEFERASIROX	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	FERASIRO 360, SICFREX, IROREST FCT, FERMATA, JADENU
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D56
Drug Class	CHELATOR
Drug Sub-class	IRON-CHELATING AGENTS

ATC Code	V03AC03
Pharmacological Class (ASHP)	IRON-CHELATING AGENTS
DRUG INFORMATION	
Dosage Form	Film-coated tablet Dispersible tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Chronic iron overload due to blood transfusions:** Initial: 14 mg/kg once daily Maintenance: Adjust dose every 3 to 6 months based on serum ferritin trends; adjust by 3.5 or 7 mg/kg/day; titrate to individual response and treatment goals. In patients not adequately controlled with 21 mg/kg/day, doses up to 28 mg/kg/day may be considered for serum ferritin levels persistently >2,500 mcg/L and not decreasing over time (doses >28 mg/kg/day are not recommended). If serum ferritin falls to <1,000 mcg/L at 2 consecutive visits, consider dose reduction (especially if dose is >17.5 mg/kg/day). If serum ferritin falls to <500 mcg/L, interrupt therapy and continue monitoring monthly. **Chronic iron overload in non-transfusion-dependent thalassemia syndromes:** Initial: 7 mg/kg once daily. Consider increasing to 14 mg/kg once daily after 4 weeks if baseline hepatic iron concentration is >15 mg Fe/g dry weight. Maintenance: Dependent upon serum ferritin measurements (monthly) and hepatic iron concentrations (every 6 months):

	If serum ferritin is <300 mcg/L: Interrupt therapy and obtain hepatic iron concentration. *If hepatic iron concentration*: • <3 mg Fe/g dry weight: Interrupt therapy; resume treatment when hepatic iron concentration is >5 mg Fe/g dry weight. • 3 to 7 mg Fe/g dry weight: Continue treatment at a dose of no more than 7 mg/kg/day. • >7 mg Fe/g dry weight: Increase dose up to 14 mg/kg/day; Maximum dose: 14 mg/kg/day.
Maximum Daily Dose Adults*	14 mg/kg/day
Dose (pediatrics)	**Children ≥10 years and Adolescents**: Initial: 7 mg/kg once daily; after 4 weeks, if hepatic iron concentration was >15 mg Fe/g dry weight, may increase to 14 mg/kg once daily. Maintenance: Dependent upon serum ferritin measurements (monthly) and LIC (every 6 months). *If serum ferritin is <300 mcg/L*: Interrupt therapy and obtain LIC. *If LIC*: • < 3 mg Fe/g dry weight: Interrupt therapy; resume treatment when LIC is >5 mg Fe/g dry weight. • 3 to 7 mg Fe/g dry weight: Continue treatment at a dose ≤7 mg/kg/day. • > 7 mg Fe/g dry weight: Increase dose to 14 mg/kg/day if not already; maximum daily dose: 14 mg/kg/day
Maximum Daily Dose Pediatrics*	14 mg/kg/day
Adjustment	**Altered Kidney Function:** **Renal impairment at treatment initiation:** eGFR >60 mL/minute/1.73 m^2: No dosage adjustment necessary.

	eGFR 40 to 60 mL/minute/1.73 m^2: Initial: Reduce dose by 50%. eGFR <40 mL/minute/1.73 m^2: Use is contraindicated. **Renal toxicity during treatment:** *Transfusional iron overload:* For increase in serum creatinine ≥33% above the average baseline, repeat serum creatinine within 1 week; if still elevated by ≥ 33%: Reduce daily dose by 7 mg/kg. eGFR <40 mL/minute/1.73 m^2: Discontinue treatment. *Non-transfusion-dependent thalassemia syndromes:* For increase in serum creatinine ≥33% above the average baseline, repeat serum creatinine within 1 week; if still elevated by ≥33%: Jadenu: Interrupt therapy if the dose is 3.5 mg/kg; reduce dose by 50% if the dose is 7 or 14 mg/kg All patients: eGFR <40 mL/minute/1.73 m^2: Discontinue treatment. **Hepatic Impairment:** **Hepatic impairment at treatment initiation:** <u>Mild impairment (Child-Pugh class A):</u> No dosage adjustment necessary; monitor closely for efficacy and for adverse reactions requiring dosage reduction. <u>Moderate impairment</u> (Child-Pugh class B): Initial: Reduce dose by 50%; monitor closely for efficacy and for adverse reactions requiring dosage reduction. <u>Severe impairment (Child-Pugh class C):</u> Avoid use.

	Hepatic toxicity during treatment: Severe or persistent increases in transaminases/bilirubin: Reduce dose or temporarily interrupt treatment.
Prescribing edits*	MD, PA
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a physician specialized in the management of thalassemia (e.g. hematologist).
PA (Prior Authorization)[13]	Treatment should only be initiated with evidence of chronic iron overload (hepatic iron concentration ≥ 5 mg Fe/g dry weight and serum ferritin > 300 mcg/L).
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** proteinuria, abdominal pain, nausea, vomiting. **Most serious**: granulocytosis, anemia, neutropenia, thrombocytopenia, respiratory tract infection.
Drug Interactions*	**Category X:** Aluminum Hydroxide, Amodiaquine, Betibeglogene Autotemcel, Fezolinetant.
Special Population	**Older adult**: Use with caution due to the higher incidence of toxicity (eg, hepatotoxicity) and fatal reactions during use; monitor elderly patients closely. **Pediatrics**: Deferasirox is associated with serious and fatal adverse reactions in pediatric patients, usually associated with volume depletion or with

	continued doses of 14 to 28 mg/kg/day (Jadenu) when body iron burden was approaching or in the normal range. Interrupt treatment in pediatric patients with transfusional iron overload with acute illnesses which may cause volume depletion (e.g., diarrhea, vomiting, prolonged decreased oral intake) and monitor more frequently; resume treatment as appropriate based on renal function assessment and when oral intake and volume status are normal. For patients with non-transfusion-dependent thalassemia (NTDT) syndromes with acute illness which may cause volume depletion, increase monitoring frequency and consider dose interruption until oral intake and volume status are normal. Monitor liver and renal function more frequently during volume depletion and in patients receiving doses of 14 to 28 mg/kg/day (Jadenu) when iron burden is approaching the normal range. Use the minimum effective dose to achieve and maintain a low iron burden.
Pregnancy	Information related to the use of deferasirox in pregnant women is limited and, in some cases, treatment was discontinued once pregnancy was discovered.
Lactation	It is not known if deferasirox is present in breast milk. Deferasirox was not detected in the breast milk of one woman 2 hours after a dose; adverse events were not observed in her exclusively breastfed infant. Maternal dosing started 1 week after delivery and infant monitoring continued for 30 days.

	Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue the drug, taking into account the importance of treatment to the mother.
Contraindications	• Known hypersensitivity to deferasirox or any component of the formulation; • eGFR <40 mL/minute/1.73 m^2 • Poor performance status; • High-risk myelodysplastic syndromes; advanced malignancies; • Platelet counts <50,000/mm^3 • CrCl <60 mL/minute; • Patients with other hematological and nonhematological malignancies who are not expected to benefit from chelation therapy (due to rapid progression of their disease).
Monitoring Requirements	**Transfusional iron overload:** Serum ferritin (baseline, monthly thereafter, and with dose increases), CBC with differential (monthly), serum electrolytes (baseline and with dose increases), renal function including serum creatinine (in duplicate at baseline), and eGFR (baseline); monitor weekly during the first month after initiation or modification of therapy and then monthly thereafter and with dose increases; liver function including serum transaminases (ALT/AST) and bilirubin (baseline, every 2 weeks for the first month, then at least monthly, and with dose increases); urinalysis (baseline and with dose increases), including urine protein (monthly); monitor cumulative number of RBC units received.

	Non-transfusion-dependent thalassemia syndromes: Liver iron concentration (either by biopsy or other approved method; baseline, then every 6 months and as clinically indicated); serum ferritin (at least 2 measurements 1 month apart prior to treatment and then monthly), CBC with differential (monthly), serum electrolytes (baseline and with dose increases); renal function including serum creatinine (in duplicate at baseline), and eGFR (baseline); monitor weekly during the first month after initiation or modification of therapy and then monthly thereafter and with dose increases; serum transaminases (ALT/AST) and bilirubin (baseline, every 2 weeks for the first month, and then at least monthly and with dose increases); urinalysis (baseline and with dose increases). **All patients:** Monitor blood glucose more frequently in patients with diabetes. Auditory examination (baseline, annually, and prior to dose increases); ophthalmic examination (including slit lamp examinations and dilated fundoscopy; baseline, annually, and prior to dose increases). Monitor for changes in eGFR and for signs of renal tubular toxicity weekly during the first month; monitor liver function and renal function more frequently in pediatric patients receiving doses 14 to 28 mg/kg/day (Jadenu) and when iron burden is approaching normal. Monitor for toxicities more frequently in elderly patients, in pediatric patients experiencing volume depletion or overchelation, and in patients receiving concomitant nephrotoxic drugs.

	Monitor for signs/symptoms of dermatologic toxicity, GI ulcers, hemorrhage, and /or hypersensitivity.
Precautions	***Concerns related to adverse effects:*** Auditory disturbances: Decreased hearing and high-frequency hearing loss have been reported (rare) with deferasirox; perform auditory testing prior to initiation and regularly (every 12 months) during use; if abnormalities develop, monitor more closely and consider dose reduction or treatment interruption. Although causality is not established, auditory adverse events may be more frequent among pediatric patients receiving doses >17.5 mg/kg/day (Jadenu) when serum ferritin is <1,000 mcg/L. Bone marrow suppression: Cytopenias (including agranulocytosis, neutropenia, thrombocytopenia, and worsening anemia) have been reported (some fatal); risk may be increased in patients with preexisting hematologic disorders; monitor blood counts regularly. Interrupt treatment in patients who develop cytopenias; may reinitiate once cause of cytopenia has been determined; use contraindicated if platelet count <50,000/mm^3. Dermatologic toxicity: May cause skin rash (dose-related); mild to moderate rashes may resolve without treatment interruption; for severe rash, interrupt and consider restarting at a lower dose with dose escalation and oral steroids. Severe and potentially life-threatening skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, erythema multiforme, and drug reaction with

	eosinophilia and systemic symptoms (DRESS), have also been reported. If severe skin reactions are suspected, discontinue immediately and evaluate; do not reintroduce therapy. Gastrointestinal reactions: **[US Boxed Warning]: GI hemorrhages (including fatalities) may occur; observed more frequently in elderly patients with advanced hematologic malignancies and/or low platelet counts; discontinue treatment for suspected GI hemorrhage or ulceration.** Nonfatal upper GI irritation, hemorrhage, and ulceration (sometimes complicated with GI perforation, including fatalities) have been reported. Use caution with concurrent medications that may increase risk of adverse GI effects (eg, NSAIDs, corticosteroids, anticoagulants, oral bisphosphonates). Monitor patients closely for signs/symptoms of GI ulceration/bleeding. Hepatic failure: **[US Boxed Warning]: Hepatic injury and failure (including fatalities) may occur. Monitor transaminases and bilirubin at baseline, every 2 weeks for 1 month, then at least monthly thereafter. Avoid use in patients with severe (Child-Pugh class C) hepatic impairment; initial dose reduction is required in patients with moderate (Child-Pugh class B) hepatic impairment.** Patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) impairment may have a higher risk for toxicities. Hepatotoxicity may be more common in patients >55 years. Patients with significant comorbidities (eg, liver cirrhosis and multiorgan

	failure) may experience hepatic failure more commonly. Acute liver injury and failure, including fatal outcomes, have occurred in pediatric patients. Hepatic failure associated with acute kidney injury has occurred in pediatric patients at risk for overchelation during states of volume depletion. Interrupt treatment if acute liver injury or acute kidney injury are suspected, and during volume depletion. Monitor liver and renal function more frequently in pediatric patients who are receiving 14 to 28 mg/kg/day (Jadenu) when iron burden is approaching normal. Use the minimum effective dose to achieve and maintain a low iron burden. Monitor liver function tests (ALT, AST, and bilirubin) prior to treatment initiation, every 2 weeks during the first month, and monthly thereafter; consider dose reduction or treatment interruption for severe or persistent elevations. Hypersensitivity: Hypersensitivity reactions, including severe reactions (anaphylaxis and angioedema) have been reported; onset is usually within the first month of treatment. Discontinue if reaction is severe and do not reintroduce patients with previous hypersensitivity reactions due to risk of anaphylactic shock. -Ocular disturbances: Lens opacities, cataracts, intraocular pressure elevation, and retinal disorders have been reported (rare) with use; perform ophthalmic testing prior to initiation and regularly (every 12 months) during use; if abnormalities develop, monitor more closely and consider dose reduction or treatment interruption.

	Renal failure: **[US Boxed Warning]: Deferasirox may cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders. Evaluate renal function in all patients at baseline and prior to deferasirox dose increases. Deferasirox is contraindicated in adult and pediatric patients with eGFR <40 mL/min/1.73 m^2. Monitor serum creatinine in duplicate prior to treatment initiation and at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, and then at least monthly. Reduce the starting dose in patients with preexisting renal disease. Increase the monitoring frequency during treatment and modify the dose for patients with an increased risk of renal impairment, including use of concomitant nephrotoxic drugs, and pediatric patients with volume depletion or overchelation.** Monitor serum creatinine and/or eGFR more frequently if creatinine levels are increasing. Use the minimum effective dose necessary to establish and maintain a low iron burden and monitor renal function frequently. Individualize dose titration based on improvement in renal injury. Initial dose reductions are required in patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2); use with caution in pediatric patients with eGFR of 40 to 60 mL/minute/1.73 m^2. Deferasirox may cause acute kidney

	injury including renal failure requiring dialysis (with fatal outcomes); based on postmarketing experience, most fatalities have occurred in patients with multiple comorbidities and who were in advanced stages of hematological disorders. In studies, deferasirox-treated patients with no preexisting renal disease experienced dose-dependent mild, nonprogressive increases in serum creatinine and proteinuria. Preexisting renal disease and concomitant use of other nephrotoxic drugs may increase the risk of acute kidney injury. Acute illnesses associated with volume depletion and overchelation may increase the risk of acute kidney injury in pediatric patients. In pediatric patients, small decreases in eGFR may result in increased deferasirox exposure, particularly in younger patients (<7 years of age); without dose reduction or treatment interruption, may result in worsening renal function and further increases in deferasirox exposure. Renal tubular toxicity, including acquired Fanconi Syndrome, has been reported, most commonly in pediatric patients with beta-thalassemia and serum ferritin levels <1,500 mcg/L. Evaluate renal glomerular and tubular function prior to treatment initiation and dose increases. Monitor electrolytes and urinalysis to evaluate renal tubular function. Monitor all patients for changes in eGFR and for renal tubular toxicity weekly during the first treatment month, after treatment modifications, and at least monthly thereafter; consider dosage reduction or interruption of therapy in patients with

	abnormalities in levels of markers of renal tubular function or if clinically indicated. Monitor serum ferritin monthly (to evaluate for overchelation). Monitor renal function more frequently in patients with preexisting renal disease or decreased renal function. Interrupt treatment and monitor renal function more frequently in pediatric patients during acute illnesses resulting in volume depletion (eg, diarrhea, vomiting, or prolonged decreased oral intake); to prevent renal injury, promptly correct fluid deficits; resume treatment as appropriate when oral intake and volume status are normal (based on renal function assessment).
Black Box Warning	**Renal failure:** Deferasirox can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders. Evaluate baseline renal function prior to starting or increasing deferasirox dosing in all patients. Deferasirox is contraindicated in adult and pediatric patients with eGFR less than 40 mL/min/1.73 m^2. Measure serum creatinine in duplicate prior to initiation of therapy. Monitor renal function at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, and then at least monthly. Reduce the starting dose in patients with preexisting renal disease. During therapy, increase the frequency of monitoring and modify the dose for patients with an increased risk of renal impairment, including use of

	concomitant nephrotoxic drugs, and pediatric patients with volume depletion or overchelation. **Hepatic failure:** Deferasirox can cause hepatic injury, including hepatic failure and death. Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter. Avoid use of deferasirox in patients with severe (Child-Pugh class C) hepatic impairment and reduce the dose in patients with moderate (Child-Pugh class B) hepatic impairment. **Gastrointestinal hemorrhage:** Deferasirox can cause GI hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts. Monitor patients and discontinue deferasirox for suspected GI ulceration or hemorrhage.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of thalassemia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for deferasirox.**

Table 15. Deferasirox HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Deferasirox	NICE	N/A
	CADTH[20]	April 2007: The Canadian Expert Drug Advisory Committee (CEDAC) recommends that deferasirox be listed for

		patients who require iron chelation but in whom deferoxamine is contraindicated. While deferasirox has been shown to be effective in reducing iron stores in patients with chronic iron overload, it is uncertain if it is as effective, and it may be associated with more adverse events as compared with deferoxamine. However, the committee recognized the need for a treatment alternative in patients for whom deferoxamine is not a therapeutic option due to contraindications. The daily cost of deferoxamine ranges from $40 to $158 and this is significantly greater than the cost of deferoxamine ($20 to $84 per day). An economic evaluation submitted by the manufacturer reported an incremental cost-effectiveness of deferasirox of $67,595 per QALY. However, the evaluation assumed an improved quality of life and higher rate of treatment compliance with deferasirox versus deferoxamine, and this has not been demonstrated in clinical trials.
	HAS[21]	May 2014: Given its oral administration: • the failure to strictly demonstrate the non-inferiority of the efficacy of EXJADE relative to DESFERAL on the primary efficacy endpoint, • a sustained rate of adverse effect reporting more than 6 years after the Marketing Authorization, • the seriousness of the adverse effects observed, - the need to continue long-term monitoring of renal safety, especially in children, • the lack of any demonstration of the impact of EXJADE on compliance and quality of life observed under actual conditions of use, • the lack of available data on the possibility of retreatment in patients who reaccumulate iron after having achieved a satisfactory body iron level, The Committee considers that the improvement in actual benefit of EXJADE is:

		• minor (level IV) relative to deferoxamine (DESFERAL) in the treatment of chronic iron overload due to frequent blood transfusions (>7 ml/kg/month of packed red blood cells) in patients with beta thalassemia major aged 6 years and older.
		• moderate (level III) in the treatment of chronic iron overload due to blood transfusions when deferoxamine (DESFERAL) therapy is contraindicated or inadequate in the following patient groups:
		  ○ with other types of anemia,
		  ○ aged 2 to 5 years,
		  ○ with beta thalassemia major with iron overload due to infrequent blood transfusions (< 7 mL/kg/month of packed RBCs).
		In the situation where FERRIPROX can be used (iron overload in patients who have thalassemia major for whom a treatment with deferoxamine is contraindicated or inadequate), the Transparency Committee cannot rule on the respective performances of the two medications due to lack of comparative data.
		
		<u>January 2014</u>:
		The Committee finds that actual benefit of EXJADE is substantial in the extension of indication "treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older". The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the extension of indication "treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassemia

		syndromes aged 10 years and older" and at the dosages in the Marketing Authorization. Proposed reimbursement rate: 65%.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Deferasirox

Deferasirox is recommended as first-line treatment of thalassemia. It is given as 14 mg/kg once daily. Consider increasing after 4 weeks if baseline hepatic iron concentration is >15 mg Fe/g dry weight. Its use is backed up by several HTA bodies namely CADTH if deferoxamine is contraindicated.

2.2 Activin Receptor Ligand Trap

2.2.1 Luspatercept

Information on luspatercept is detailed in the table below[22,23] :

Table 16. Luspatercept Drug Information

SCIENTIFIC NAME LUSPATERCEPT	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	REBLOZYL
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D56
Drug Class	ERYTHROID MATURATION AGENTS
Drug Sub-class	ACTIVIN RECEPTOR LIGAND TRAP
ATC Code	QB03XA
Pharmacological Class (ASHP)	ACTIVIN RECEPTOR LIGAND TRAP, HEMATOPOIETIC AGENT
DRUG INFORMATION	
Dosage Form	Powder for solution for injection
Route of Administration	Subcutaneous use

Dose (Adult) [DDD]*	**Initial**: 1 mg/kg once every 3 weeks. **Titrate dose based on insufficient response** • Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1 mg/kg: Increase to 1.33 mg/kg q3Weeks • Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg: Increase to 1.75 mg/kg q3Weeks • Do not increase dose more frequently than q6Weeks (2 doses) or beyond maximum dose of 1.75 mg/kg • No reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.75 mg/kg: Discontinue treatment **Dosage modifications for predose Hgb levels or rapid Hgb rise** • Predose hemoglobin ≥11.5 g/dL in absence of transfusions: Interrupt dose; restart when Hgb ≤11 g/dL • Increase in hemoglobin >2 g/dL within 3 weeks (in the absence of transfusions) **and** *Current dose is 1.25 mg/kg: Reduce dose to 1 mg/kg once every 3 weeks *Current dose is 1 mg/kg: Reduce dose to 0.8 mg/kg once every 3 weeks *Current dose is 0.8 mg/kg: Reduce dose to 0.6 mg/kg once every 3 weeks *Current dose is 0.6 mg/kg: Discontinue luspatercept
Maximum Dose Adults*	1.25 mg/kg once every 3 weeks
Dose (pediatrics)	Safety and efficacy not established.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** *eGFR 30 to 89 mL/minute/1.73 m^2: There are no dosage adjustments

	provided in the manufacturer's labeling; however, no clinically significant pharmacokinetic differences were observed in patients with mild to moderate kidney impairment. *eGFR <30 mL/minute/1.73 m^2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits*	AGE, MD, PA
AGE (Age Edit)	For use in adults 18 years and above.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a physician specialized in the management of thalassemia (e.g. hematologist).
PA (Prior Authorization)[13]	Coverage may be provided with a diagnosis of anemia due to beta thalassemia and the following criteria is met: • Must have a diagnosis of beta thalassemia or Hemoglobin E/beta-thalassemia • Must NOT have a diagnosis of Hemoglobin S/beta-thalassemia or alpha-thalassemia (e.g. Hemoglobin H) • Member requires regular red blood cell (RBC) transfusions (at least 6 RBC units in the past 6 months with no transfusion-free period greater than 35 days)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A

SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** hypertension, abdominal pain, nausea, ostealgia. **Most serious**: Thromboembolism, Neutropenia, Osteoarthritis, Urinary tract infection, Hyperuricemia.
Drug Interactions*	**Category X**: N/A
Special Population	N/A
Pregnancy	Based on data from animal reproduction studies, in utero exposure to luspatercept may cause fetal harm.
Lactation	It is not known if luspatercept is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 3 months after the last luspatercept dose.
Contraindications	Hypersensitivity to luspatercept or any component of the formulation.
Monitoring Requirements	Assess Hb prior to each luspatercept dose. Evaluate pregnancy status prior to initiation (in patients who could become pregnant). Monitor blood pressure prior to each dose and as clinically necessary. Monitor for signs/symptoms of thromboembolism. Monitor patients with beta thalassemia at therapy initiation and during treatment for signs/symptoms of extramedullary hematopoietic mass and complications that may result. The American Society of Clinical Oncology hepatitis B virus (HBV) screening and management provisional clinical opinion recommends HBV screening with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B

	surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up.
Precautions	***Concerns related to adverse effects:*** Extramedullary hematopoietic masses: Extramedullary hematopoietic (EMH) masses were observed in a small percentage of patients with transfusion dependent beta thalassemia receiving luspatercept; symptoms of spinal cord compression due to EMH masses occurred in some patients. EMH masses were also observed in patients with nontransfusion-dependent beta thalassemia (not an approved indication). Risk factors for development of EMH masses may include history of EMH masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL); signs/symptoms may vary based on the anatomical location. Hypertension: Hypertension has been reported, including grade 3 and 4 events. Patients with normal baseline BP have developed elevated systolic BP (≥130 mm Hg) and/or elevated diastolic BP (≥80 mm Hg). Thromboembolic events: Thromboembolic events, including deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic strokes, have been reported in a small number of patients with beta thalassemia receiving luspatercept in clinical trials. Patients with known risk

	factors for thromboembolism such as splenectomy or concomitant use of hormone therapy may be at increased risk of thromboembolic events.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of thalassemia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for luspatercept.**

Table 17. Luspatercept HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Luspatercept	NICE[24]	November 2022: NICE is unable to make a recommendation about the use in the NHS of luspatercept for treating anemia caused by beta-thalassemia in adults. This is because BMS has confirmed that it does not intend to make an evidence submission for the appraisal. BMS considers that there is not enough evidence to provide a submission for this appraisal.
	CADTH[25]	June 2021: The CADTH Canadian Drug Expert Committee (CDEC) **recommends that luspatercept should be reimbursed for the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with beta-thalassemia**, only if the conditions below are met: *Initiation*: • Adults with RBC transfusion-dependent anemia associated with beta-thalassemia. • Patients must be receiving regular transfusions, defined as: o 6 to 20 RBC units in the 24 weeks prior to initiating treatment with luspatercept, and

		○ No transfusion-free period greater than 35 days in the 24 weeks prior to initiating treatment with luspatercept. *Renewal*: • Patients should be assessed for a response to luspatercept every 6 months. ○ Initial response is defined as a ≥ 33% reduction in transfusion burden (RBC units/time) and should be compared to the pre-treatment baseline RBC transfusion burden, measured over 24 weeks before initiating treatment with luspatercept. ○ At each subsequent assessment, a reduction in transfusion burden of ≥ 33% compared to the pre-luspatercept transfusion burden must be maintained. *Discontinuation*: Luspatercept should be discontinued if a patient does not respond after 9 weeks of treatment (3 doses) at the maximum dose. *Prescribing*: • The patient should be under the care of a hematologist with experience in managing patients with beta-thalassemia. • The maximum dose of luspatercept should not exceed 1.25 mg/kg (or 120 mg total dose) per administration. *Pricing*: Based on CADTH reanalyses, the ICER of luspatercept plus BSC compared with BSC for patients with beta-thalassemia was $659,395 per QALY, with a 0% chance of being cost-effective at a WTP threshold of $50,000 per QALY. A **price reduction of at least 85% is needed** to meet the $50,000 WTP threshold. The sponsor's submitted price of luspatercept is $2,189 per 25 mg and $6,567 per 75 mg. The recommended dose of luspatercept depends on

		treatment response; therefore, the average daily treatment ranges from $312.71 to $416.95, while the average annual cost of treatment is between $113,828 and $151,771 per patient. CADTH estimated the incremental cost-effectiveness ratio (ICER) of luspatercept compared with BSC to be $659,395 per QALY, with a 0% probability of being cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold at the price submitted by the sponsor. A price reduction of 85% would be required for luspatercept to be cost-effective at this threshold. Scenario analyses were conducted to assess the impact of clinical uncertainty with luspatercept (examining the predictive value of serum ferritin, mortality benefit of luspatercept, and treatment durability of luspatercept). The scenario analyses resulted in ICERs greater than $1 million per QALY.
	HAS[26]	August 2021: Unfavorable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia. The committee deems that the clinical benefit of luspatercept is insufficient to justify public funding cover in the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Luspatercept

Luspatercept is considered when individuals with beta-thalassemia become transfusion-dependent and experience complications associated with chronic transfusions. It is aimed at reducing the need for blood transfusions and improving the overall management of anemia in these individuals. It is given as 1 mg/kg once every 3 weeks. Its use is backed up by HTA body namely CADTH; other HTA bodies reject its reimbursement in others; these HTA bodies include HAS. The use of Luspatercept is limited by the elevated risk of urinary tract infections, thromboembolism, and ischemic stroke.

2.3 Antineoplastic Agents

2.3.1 Hydroxyurea (Hydroxycarbamide)

Table 18. Hydroxyurea Drug Information

SCIENTIFIC NAME HYDROXYUREA (Hydroxycarbamide)	
Trade Name(s) on Saudi Market	Cureaml; Xromi
SFDA Classification	Prescription
SFDA approved Indication	No, off-label
FDA approved / off label	No, off-label
EMEA approved / off label	No, off-label
MHRA approved / off label	No, off-label
PMDA approved / off label	No, off-label
Indication (ICD-10)	D56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite
SFDA Registration Number (New)	Cureaml: 1406222189 Xromi: 0512222977
ATC Code	L01XX05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Capsule (Cureaml); Oral Solution (Xromi)
Route of Administration	Oral
Dose (Adult) [DDD]*	Dose ranging from 10 mg/kg/day to 20 mg/kg/day[10]
Dose (Pediatrics)	N/A
Adjustment	Reduce the dose by 50% in patients with creatinine clearance < 60 mL/min
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a physician specialized in the management of thalassemia (e.g. hematologist).
PA (Prior Authorization)	N/A

QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
Maximum Daily Dose Adults*	35 mg/kg/day
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hematological (neutropenia), gastrointestinal symptoms, anorexia, and infections - Most serious: Thrombocytopenia, viral infections, fever, secondary leukemia in long-term use
Drug Interactions*	Rotavirus Vaccine (Contraindications) Live Vaccines (Contraindications) Stavudine (Major-Increased risk of peripheral neuropathy, fatal pancreatitis and hepatotoxicity) Didanosine (Major-Increased risk of pancreatitis and hepatotoxicity)
Special Population	Renal Impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Excreted in human milk; advise not to breastfeed
Contraindications	Prior hypersensitivity to drug or any of its products
Monitoring Requirements	CBC every 2 weeks
Precautions	- Myelosuppression - Hemolytic anemia - Malignancies - Embryo-fetal toxicity - Vasculitic toxicities - Live vaccines - Risks with concomitant use of antiretroviral drugs - Macrocytosis

	- Pulmonary toxicity
Black Box Warning	- Myelosuppression - Malignancies
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of thalassemia treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Hydroxyurea

Hydroxyurea (hydroxycarbamide) is used off-label for the management of transfusion-dependent beta-thalassemia. It is used as a single intervention with no other treatment apart from blood transfusions. It is given as a single daily oral agent ranging from 10 to 20 mg/kg/day. The duration of treatment should be between 3–6 months before judging its efficacy. HU was associated with a significant decrease in transfusion need (complete cessation in infrequently transfused patients and/or ≥50% reduction in transfusion-dependent patients) and/or an increase in Hb >1 g/dL from baseline with a RR of 46%[10,27].

2.4 Other Drugs

This section details drugs that are used for the management of thalassemia but are not currently SFDA-registered.

2.4.1 Betibeglogene Autotemcel Gene Therapy for Non-β^0/β^0 Genotype β-Thalassemia

Betibeglogene autotemcel (beti-cel) gene therapy for transfusion-dependent β-thalassemia contains autologous CD34+ hematopoietic stem cells and progenitor cells transduced with the BB305 lentiviral vector encoding the β-globin ($\beta^{A\text{-}T87Q}$) gene. Treatment with beti-cel resulted in a sustained HbA^{T87Q} level and a total hemoglobin level that was high enough to enable transfusion independence in most patients with a non-β^0/β^0 genotype, including those younger than 12 years of age[28]. No HTA data is available on the use of beti-cel in thalassemia. In December 2022, the National Institute for Health and Care Excellence (NICE) in the UK discontinued the appraisal as no further information had been received from the company[29].

2.4.2 Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

Exagamglogene Autotemcel (exa-cel) (Casgevy™) gene therapy contains autologous CD34+ hematopoietic stem cells and progenitor non-viral cell therapy designed to reactivate fetal hemoglobin (HbF) via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of BCL11A in patients. Approval was based on results from a pre-specified interim analysis of the CLIMB THAL-111 trial, an ongoing, 24-month (mo), phase 3 trial of exa-cel in pts age 12-35y with TDT and a history of ≥100 mL/kg/y or ≥10 U/y packed red blood cell (RBC) transfusions in the 2y before screening. Treatment with exa-cel resulted in a sustained HbF level and a total hemoglobin level that was high enough to enable transfusion independence in most patients with TDT[30]. No HTA data is available on the use of exa-cel in thalassemia.

2.4.3 Mitapivat

Mitapivat (Pyrunkynd®) is a pyruvate kinase activator. Mitapivat was approved by the FDA in February 2022 for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency and by the EMA in November 2022 for the treatment of pyruvate kinase deficiency (PK deficiency) in adult patients.[31,32]

Mitapivat for the treatment of thalassemia was assessed in a phase 2 open-label, multicenter study published in Lancet in August 2022. Patients were eligible if they were aged 18 years or older, with NTDT (including β-thalassemia with or without α-globin gene mutations, hemoglobin E β-thalassemia, or α-thalassemia), and a baseline hemoglobin concentration of 10.0 g/dL or lower. During a 24-week core period, mitapivat was administered orally at 50 mg twice daily for the first 6 weeks followed by an escalation to 100 mg twice daily for 18 weeks thereafter. The primary endpoint was hemoglobin response (a ≥ 1.0 g/dL increase in hemoglobin concentration from baseline at one or more assessments between weeks 4 and 12). Of the 20 enrolled patients, 16 (80% [90% CI 60-93]) had a hemoglobin response ($p < 0.0001$), five (100%) of five with α-thalassemia and 11 (73%) of 15 with β-thalassemia. 17 (85%) patients had a treatment-emergent adverse event, and 13 had a treatment-emergent event that was considered to be treatment related[33].

On January 3, 2024, Agios announced that the phase 3 ENERGIZE study of mitapivat met its primary endpoint and both key secondary endpoints in adults with non-transfusion-dependent alpha- or beta-thalassemia. A total of 194 patients were enrolled in the study, with 130 randomized to mitapivat 100 mg twice-daily (BID) and 64 randomized to matched placebo. 122 (93.8%) in the mitapivat arm and 62 (96.9%) in the placebo arm completed the 24-week double-blind period of the study. 42.3%

of patients in the mitapivat arm achieved a hemoglobin response, compared to 1.6% of patients in the placebo arm (2-sided $p < 0.0001$)[34].

Agios is also advancing the fully enrolled Phase 3 ENERGIZE-T study of mitapivat in adults with transfusion-dependent alpha- or beta-thalassemia and expects to announce topline data from this 48-week study in mid-2024. Following the read-out of ENERGIZE-T, the company intends to file for regulatory approval of mitapivat as a treatment for thalassemia by the end of 2024, incorporating all available data from both studies[34].

Section 3.0 Key Recommendations Synthesis

- Individuals with moderate to severe thalassemia often require regular blood transfusions to maintain an adequate supply of healthy red blood cells.
- Transfuse red cells stored in CPD-A within one week of collection and red cells stored in additive solutions within two weeks of collection where available. (IA).
- Transfuse every 2-5 weeks, maintaining pre-transfusion hemoglobin above 95-105 g/ l or up to 110-120 g/l for patients with cardiac complications (IA).
- Keep a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient (IIA).
- Keep the post-transfusion hemoglobin below 130-150 g/l (IIA).
- Prolonged blood transfusions can lead to iron overload in the body. Iron chelation therapy, using medications such as deferoxamine, deferiprone, or deferasirox, helps remove excess iron.
- Hematopoietic stem cell transplantation (HSCT) shall be offered early in childhood especially in the presence of matched related donor.
- In thalassemia patients, HSCT is cost-effective when compared to life-long supportive therapy.
- Gene therapy is a newly approved therapy and shall be offered to patients with no available appropriate matched donor.
- Other agents for the management of thalassemia include luspatercept (approved for the treatment of anemia in adults with transfusion-dependent beta-thalassemia) and hydroxyurea (used off-label).

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of thalassemia.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

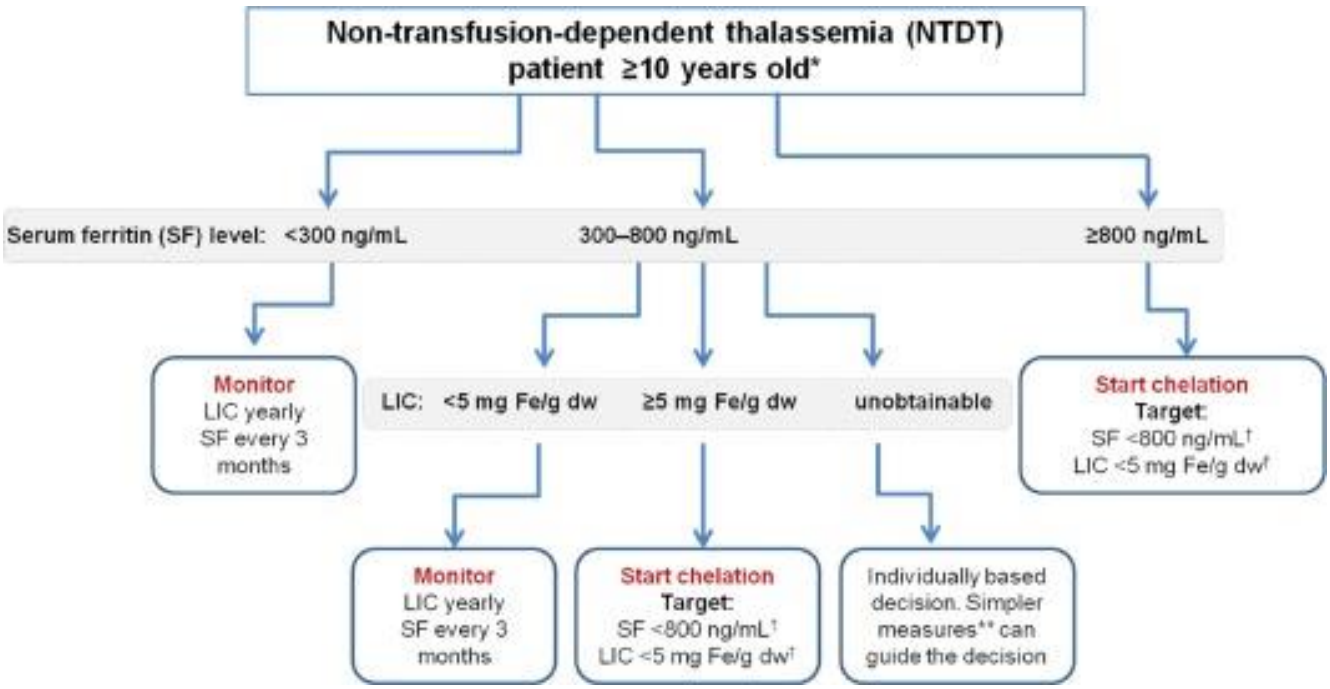
Appendix B. Level of Evidence Description

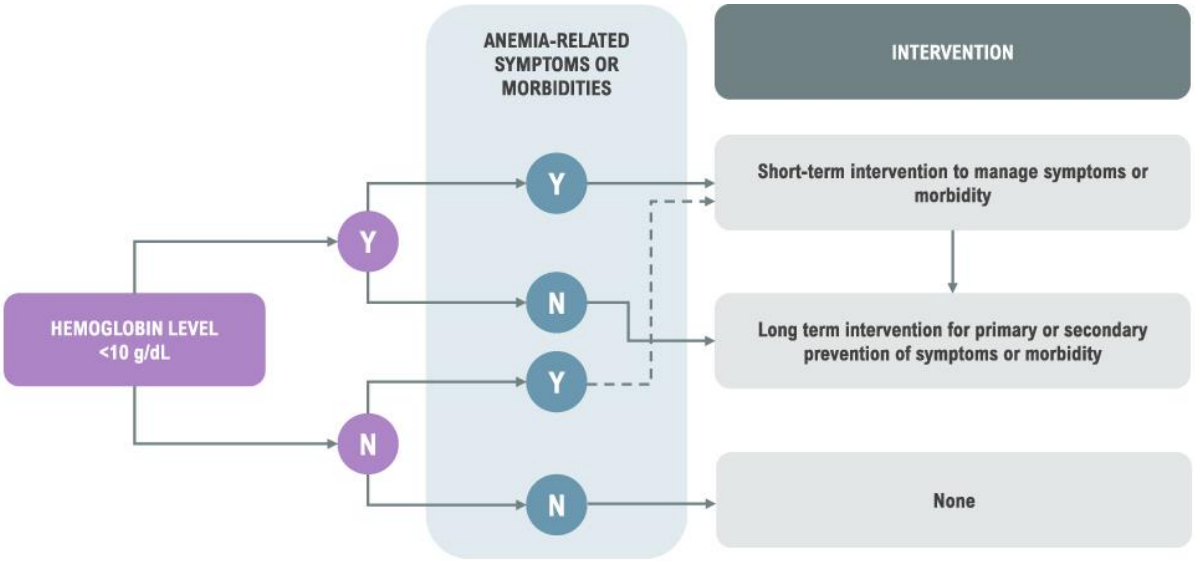
Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

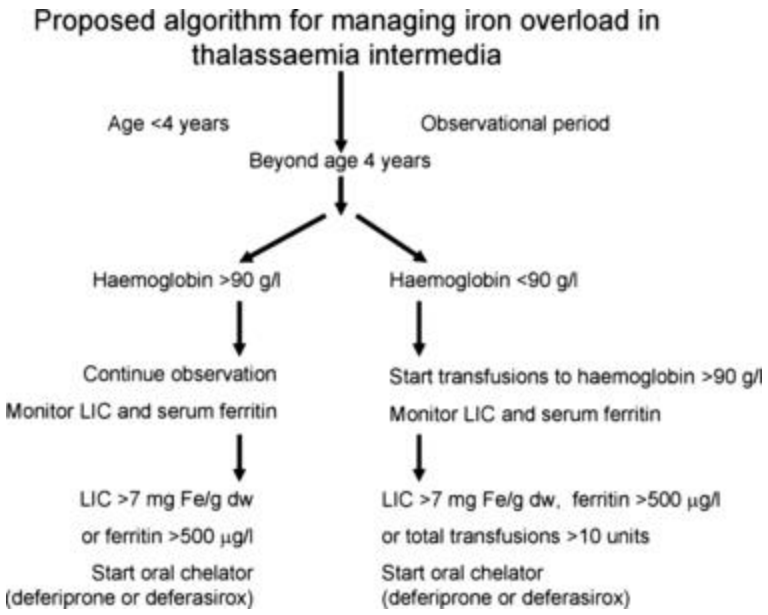
Query	Filters	Search Details	Results
(Thalassemia[MeSH Terms]) OR (Thalassemias[Title/Abstract])	Meta-Analysis, Systematic Review, in the last 1 year	("thalassemia"[MeSH Terms] OR "Thalassemias"[Title/Abstract]) AND ((y_1[Filter]) AND (meta-analysis[Filter] OR systematicreview[Filter]))	19

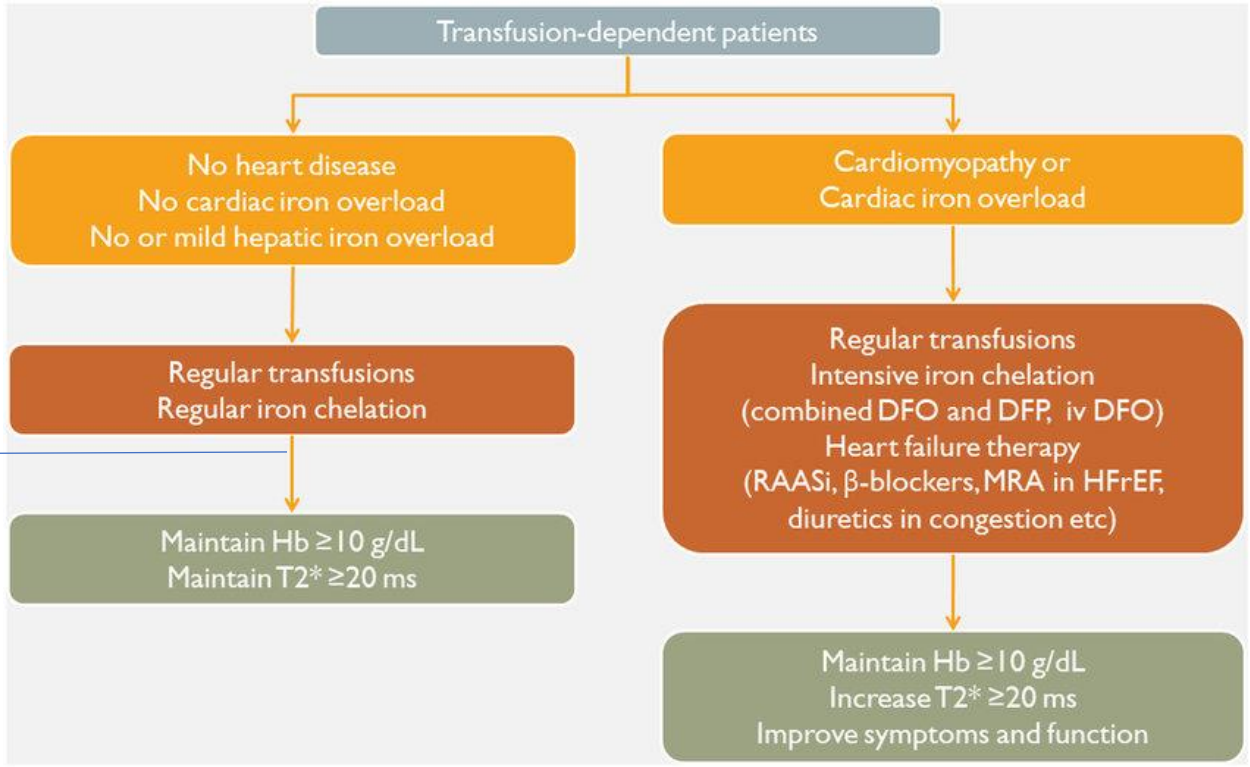
Appendix D. Treatment Algorithms





INTERVENTION	POSITIVE ATTRIBUTES	CHALLENGES
Transfusion	▪ Considerable experience from managing transfusion-dependent patients ▪ Observational data on management and prevention of morbidity and improved survival	▪ Secondary iron overload ▪ Transfusion-related reactions (alloimmunization) and infections ▪ Burden of administration and visit schedule
Hydroxyurea	▪ Evidence of erythroid response in small series and trials ▪ Oral administration ▪ Observational data on management and prevention of morbidity	▪ Concerns with long-term safety ▪ Loss of response on long-term therapy ▪ Not suitable during pregnancy
Luspatercept	▪ Evidence of erythroid response from a randomized clinical trial ▪ Improvement of morbidity (e.g., leg ulcers) in some patients included in the trials	▪ Absence of long-term data on clinical benefit ▪ Subcutaneous administration ▪ Not suitable during pregnancy





HLA typing

Matched donor :

HSCT

No Matched donor : and > 12 years Consider Gene therapy