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# DRUGS USED IN TREATMENT OF THALASSEMIA

**Arabinda Nayak*, Jay Poker, Shankar Patel, Dharmesh Vashadiya**
Atmiya Inst.of Pharmacy, Yogidhum Gurukul,Kalawad Road,Rajkot, Gujrat, India.
*Email: arabinda00717@gmail.com*

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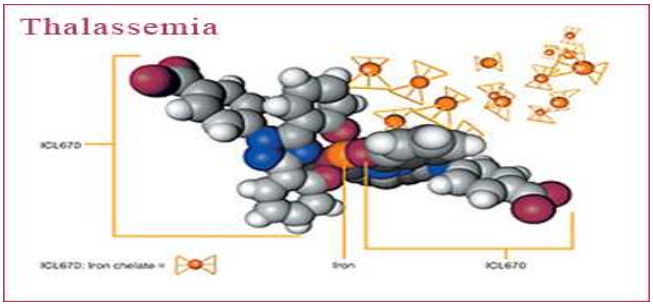
**Abstract**

Thalassaemia is an inherited condition affecting the blood. This is a blood disorder passed down through families (inherited) in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen. The disorder results in excessive destruction of red blood cells, which leads to anemia. Most of the medications used to treat thalassemia are aimed at trying to get rid of the excess iron that accumulates with the years of chronic transfusions. In a recent study, researchers in Greece found that intensive treatment with two chelator medications together was able to normalize the iron load in thalassemia patients and prevent or reverse complications due to iron overload from transfusions, including cardiac and endocrine problems. One of the chelator medications used in the study, deferiprone, is not yet approved by the FDA. It is a fatal disease that can be managed by regular and proper retaining the healthy haemoglobin in the body by medications and blood transfusion.

**Key words:** Hemoglobin, Anemia, Medications, Transfusion.

## Introduction

**Thalassemia** (British English: **thalassaemia**) is a group of inherited autosomal recessive blood disorders that originated in the Mediterranean region. In thalassemia the genetic defect, which could be either mutation or deletion, results in reduced rate of synthesis or no synthesis of one of the globin chains that make up hemoglobin. This can cause the formation of abnormal hemoglobin molecules, thus causing anemia, the characteristic presenting symptom of the thalassemias.

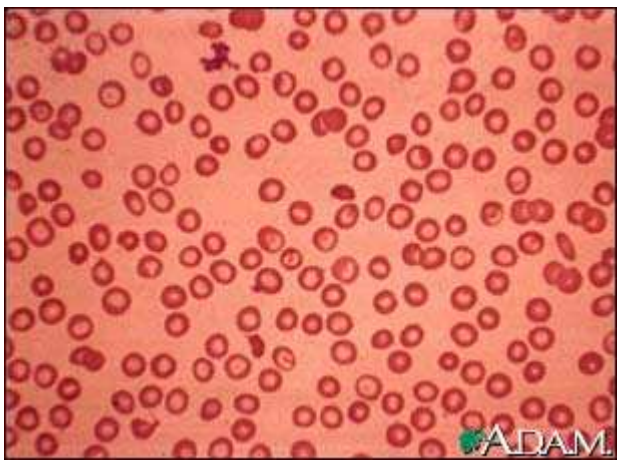



Normal hemoglobin is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. Thalassemia patients produce a *deficiency* of either α or β globin, unlike sickle-cell disease, which produces a specific mutant form of β globin.

The thalassemias are classified according to which chain of the hemoglobin molecule is affected. In α thalassemias, production of the α globin chain is affected, while in β thalassemia production of the β globin chain is affected.The β globin chains are encoded by a single gene on chromosome 11; α globin chains are encoded by two closely linked genes on chromosome 16. Thus, in a normal person with two copies of each chromosome, there are **two** loci encoding the β chain, and **four** loci encoding the α chain.As well as alpha and beta chains present in hemoglobin, about 3% of adult hemoglobin is made of alpha and delta chains. Just as with beta thalassemia, mutations that affect the ability of this gene to produce delta chains can occur.

**Carrier Detection**

**Thalassemia Minor**

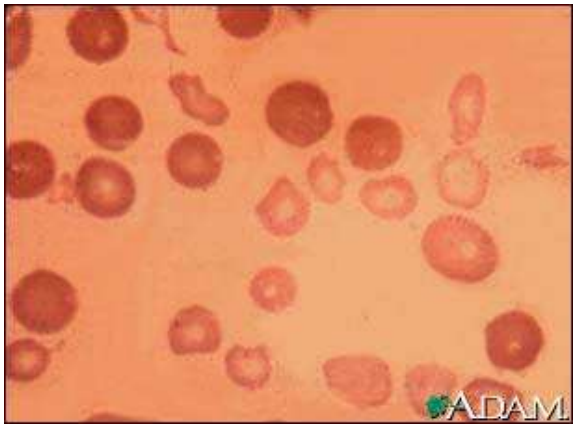



Your blood count may be a little lower than other people of your age and sex, but this produces no symptoms. You were born with this condition and you will have it all of your lifetime. There is no need for treatment and most

people who have inherited this are not sick and probably do not know they have it. A mild form of Thalassemia minor may be mistaken for iron deficiency anemia. Iron medicines are not usually necessary and will not help your anemia. They could even be harmful if taken over a long period of time.

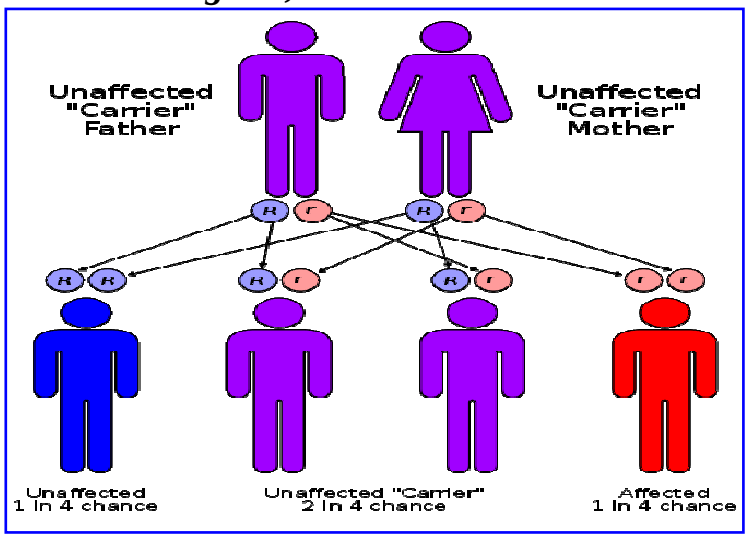
If you marry a person who does not have Thalassemia Minor, your children may have Thalassemia Minor. If you marry a person who does have Thalassemia Minor, some of your children may have Thalassemia Major. You must decide if you want to take this risk in planning your family.

**Thalassemia Major**




Thalassemia Major occurs when a person inherits two Thalassemia genes, one from each parent. Both parents must have Thalassemia Minor. When two individuals who have Thalassemia Minor marry, there is a 25% chance that any pregnancy can result in a child with Thalassemia Major. Two of four children will have Thalassemia Minor and 1 of 4 will be normal. These chances are present with each pregnancy. Some families have had only one ill child, while others have had all of their children affected.

***Figure , carrier transmission***



- **Symptoms**

Signs and symptoms of thalassemia include:

- Fatigue
- Weakness
- Shortness of breath
- Pale appearance
- Irritability
- Yellow discoloration of skin (jaundice)
- Facial bone deformities
- Slow growth
- Abdominal swelling
- Dark urine

The signs and symptoms you experience depend on the type and severity of thalassemia you have. Some babies show signs and symptoms of thalassemia at birth, while others may develop signs or symptoms during the first two years of life. Some people who have only one affected hemoglobin gene don't experience any thalassemia symptoms.

- **Treatment**

  - **Medical care**

    - ✓ Mild thalassemia : patients with thalassemia traits do not require medical or follow-up care after the initial diagnosis is made. Patients with β-thalassemia trait should be warned that their blood picture resembles iron deficiency and can be misdiagnosed. They should eschew empirical use of Iron therapy; yet iron deficiency can develop during pregnancy or from chronic bleeding. Counseling is indicated in all persons with genetic disorders, especially when the family is at risk of a severe form of disease that may be prevented.

- ✓ Severe thalassemia : patients with severe thalassemia require medical treatment, and a blood transfusion regimen was the first measure effective in prolonging life

**Treatments for mild thalassemia**.

Signs and symptoms are usually mild with thalassemia minor and little, if any, treatment is needed. Occasionally, you may need a blood transfusion, particularly after surgery, after having a baby or to help manage thalassemia complications.

- o **Treatment for moderate to severe Thalassemia**
  - ✓ **Frequent blood transfusions.** More-severe forms of thalassemia often require frequent blood transfusions, possibly every few weeks. Over time, blood transfusions cause a buildup of iron in your blood, which can damage your heart, liver and other organs. To help your body get rid of the extra iron, you may need to take medications that rid your body of extra iron.
  - ✓ **Stem cell transplant.** Also called a bone marrow transplant, a stem cell transplant may be used to treat severe thalassemia in select cases. Prior to a stem cell transplant, you receive very high doses of drugs or radiation to destroy your diseased bone marrow. Then you receive infusions of stem cells from a compatible donor. However, because these procedures have serious risks, including death, they're generally reserved for people with the most severe disease who have a well-matched donor available — usually a sibling

- ➢ **<u>Tests and diagnosis</u>**

Most children with moderate to severe thalassemia show signs and symptoms within their first two years of life. If your doctor suspects your child has thalassemia, he or she may confirm a diagnosis using blood tests.

If your child has thalassemia, blood tests may reveal:

- A low level of red blood cells
- Smaller than expected red blood cells
- Pale red blood cells

- Red blood cells that are varied in size and shape
- Red blood cells with uneven hemoglobin distribution, which gives the cells a bull's-eye appearance under the microscope

Blood tests may also be used to:

- Measure the amount of iron in your child's blood
- Evaluate his or her hemoglobin
- Perform DNA analysis to diagnose thalassemia or to determine if a person is carrying mutated hemoglobin genes

**Prenatal testing**

Testing can be done before a baby is born to find out if it has thalassemia and determine how severe it may be. Tests used to diagnose thalassemia in fetuses include:

- **Chorionic villus sampling.** This test is usually done around the 11th week of pregnancy and involves removing a tiny piece of the placenta for evaluation.
- **Amniocentesis.** This test is usually done around the 16th week of pregnancy and involves taking a sample of the fluid that surrounds the fetus.
- **Assisted reproductive technology**

  A form of assisted reproductive technology that combines pre-implantation genetic diagnosis with in vitro fertilization may help parents who have thalassemia or who are carriers of a defective hemoglobin gene give birth to healthy babies. The procedure involves retrieving mature eggs from a woman and fertilizing them with a man's sperm in a dish in a laboratory. The embryos are tested for the defective genes, and only those without genetic defects are implanted in the woman.

➔ **β-Thalassemia major diagnostic algorithm**

Patient presents with pallor, severe anemia, jaundice, and hepatosplenomegaly

Recommended evaluations

History and physical examination Complete blood count and platelets

Examination of peripheral blood smear

Diagnosis of thalassemia major based on Hb evaluation

Serum Hb (< 7 g/dL)

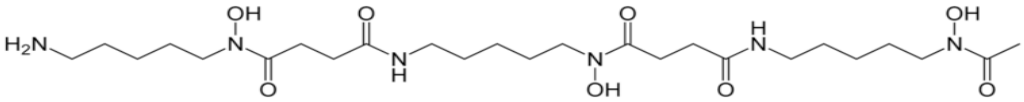
Hb electrophoresis

- **Drugs use in treatment of thalassemia.**

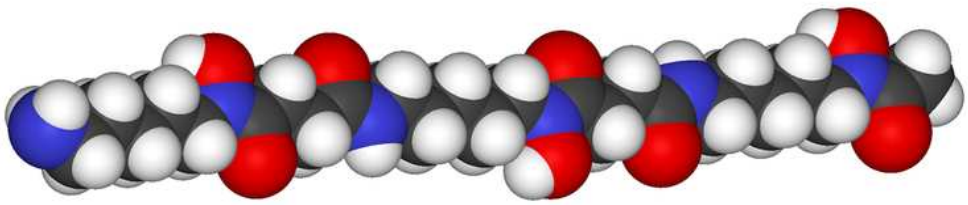
Medical therapy for beta thalassemia primarily involves iron chelation. Deferoxamine is the intravenously or subcutaneously administered chelation agent currently approved for use in the United States. Deferasirox (Exjade) is an oral iron chelation drug also approved in the US in 2005. Deferiprone is an oral iron chelator that has been approved in Europe since 1999 and many other countries. It is available under compassionate use guidelines in the United States.

**Deferoxamine**

**Brand Names: Desferal**



**Structure:**



**IUPAC Name:**

*N'*-{5-[Acetyl(hydroxy)amino]pentyl}-*N*-[5-({4-[(5-aminopentyl)(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-*N*-hydroxysuccinamide

**Generic Name:** deferoxamine (Pronunciation: de fer OX a meen)

**Chemical data:**

Molecular formula : $C_{25}H_{48}N_6O_8$

Molar mass : 560.68 g $mol^{-1}$

**Mechanism**

Deferoxamine acts by binding free iron in the bloodstream and enhancing its elimination in the urine. By removing excess iron, the agent reduces the damage done to various organs and tissues, such as the liver. A recent study also shows that it speeds healing of nerve damage (and minimizes the extent of recent nerve trauma). Deferoxamine may modulate expression and release of inflammatory mediators by specific cell types

- **What are the possible side effects of deferoxamine (Desferal)?**

Get emergency medical help if you have any of these signs of an allergic reaction: hives; joint or muscle pain; fever; headache; nausea or vomiting; difficulty breathing; swelling of your face, lips, tongue, or throat.

Stop using deferox these serious side effects: amine and call your doctor at once if you have any of ….

Fast heartbeats;

Blue lips, skin, or fingernails;

Severe, watery, bloody diarrhea with cramping;

Cough, wheezing, gasping, or other breathing problems;

Stuffy nose, fever, redness or swelling around your nose and eyes, scabbing inside your nose;

Stomach or back pain, coughing up blood;

Easy bruising or bleeding, unusual weakness;

Urinating less than usual or not at all;

Vision or hearing problems; or

Leg cramps, bone problems, or growth changes (in a child using this medication).

Keep using deferoxamine and talk to your doctor if you have any of these less serious side effects:

Numbness or burning pain anywhere in the body;

Warmth, redness, or tingly feeling under the skin;

Mild itching or skin rash;

Mild diarrhea, nausea, or upset stomach;

Dizziness;

Reddish colored urine; or

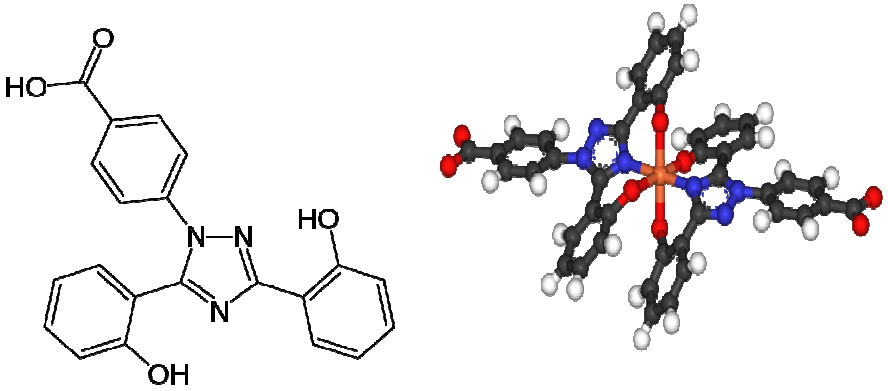
Pain, burning, swelling, redness, irritation, or a hard lump where the medicine was injected.

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome.

**Deferasirox**

**Brand Names:** Exjade

**Structure:**




IUPAC name: [4-[(3*Z*,5*E*)-3,5-bis(6-oxo-1-cyclohexa-2,4-dienylidene)-1,2,4-triazolidin-1-yl]benzoic acid

**Chemical data:**

Molecular formula : $\mathbf{C_{21}H_{15}N_3O_4}$

Molar mass : 373.362 g/mol

**Mechanism**

Exjade (deferasirox) is an orally active chelator that is selective for iron (as Fe3+). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

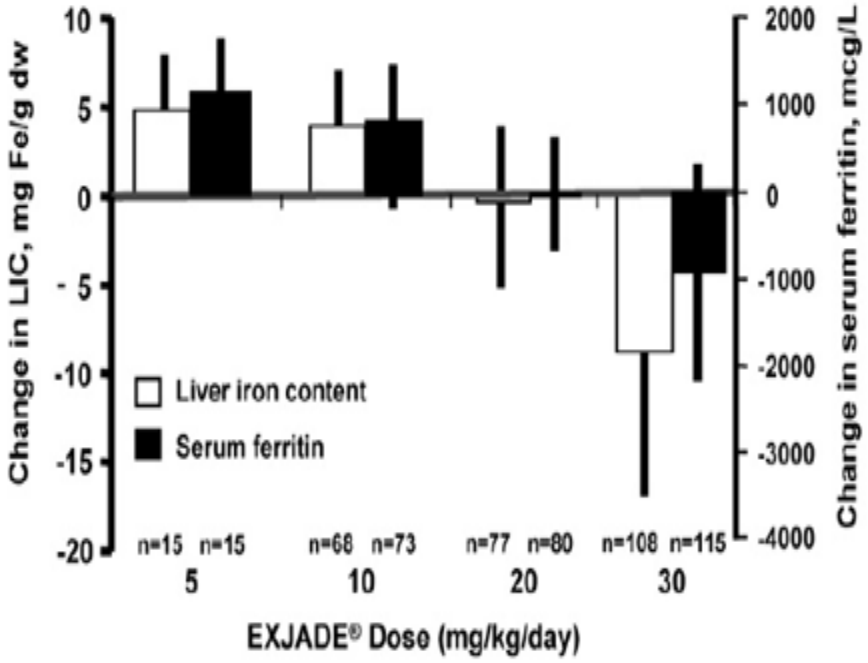



**Figure: Changes in Liver Iron Concentration and Serum Ferritin Following EXJADE (5-30 mg/kg per day) in Study 1**

- **What are the possible side effects of Deferasirox**

  Weakness or fainting, bloody or tarry stools;

  Coughing up blood or vomit that looks like coffee grounds;

  Severe stomach pain that may spread to your back;

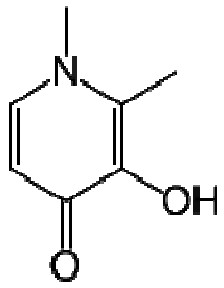
  Increased thirst and urination, loss of appetite, weakness, constipation;

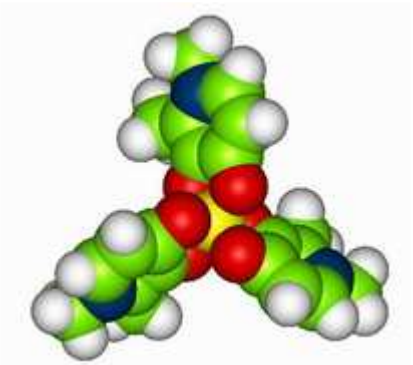
  Stop using deferasirox and get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

**Deferiprone**

**Brand Names:** Ferriprox

**Structure:**



IUPAC name: 3-hydroxy-1,2-dimethylpyridin-4(1*H*)-one

**Chemical data**:

**Molecular formula: $C_7H_9NO_2$**

**Molar mass :** 139.152 g/mol

**Mechanism:**

**Deferiprone** is a chelating agent with an affinity for ferric ion (iron III). Deferiprone binds with ferric ions to form neutral 3:1 (deferiprone:iron) complexes that are stable over a wide range of pH values. Deferiprone has a lower binding affinity for other metals such as copper, aluminum and zinc than for iron**.**

**What are the possible side effects of Deferiprone**

Chromaturia

(It is a result of the excretion of the iron in the urine.)

Agranulocytosis

Nausea,

Vomiting,

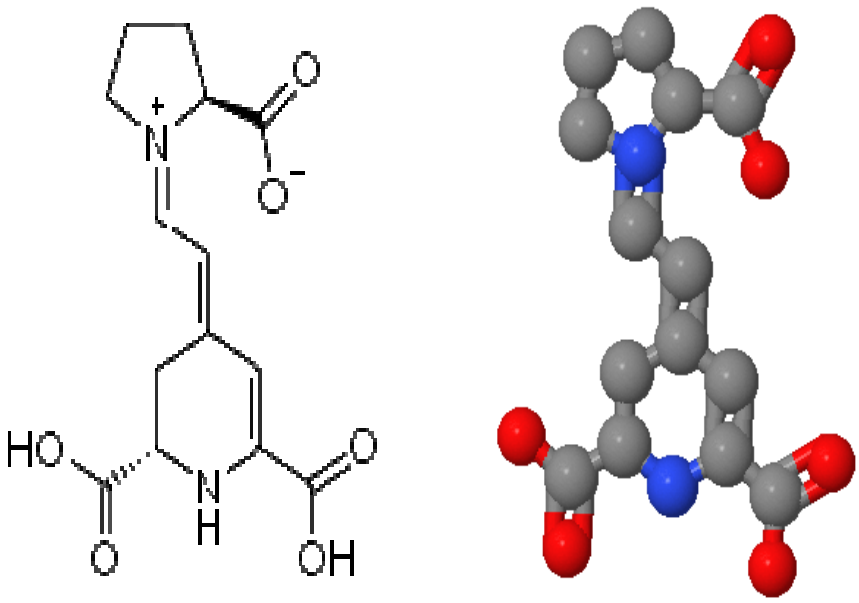
Abdominal Pain,

Alanine aminotransferase increased,

Arthralgia

Neutropenia.

**Indicaxanthin**



**IUPAC name:** 4-[2-(2-Carboxy-pyrrolidin-1-yl)-vinyl]-2,3-dihydro-pyridine-2,6-dicarboxylic acid

**Chemical data**:

**Molecular formula:** $C_{14}H_{16}N_2O_6$

**Molar mass :** 308.29 g/mol

**Mechanism:**

Indicaxanthin was assessed for its protective effects on human beta-thalassemic RBCs submitted in vitro to oxidative haemolysis by cumene hydroperoxide. Indicaxanthin at 1.0-10 microM enhanced the resistance to haemolysis dose-dependently. In addition, it prevented lipid and haemoglobin (Hb) oxidation, and retarded vitamin E and GSH depletion. After ex vivo spiking of blood from thalassemia patients with indicaxanthin, the phytochemical was recovered in the soluble cell compartment of the RBCs. A spectrophotometric study showed that indicaxanthin can reduce perferryl-Hb generated in solution from met-Hb and hydrogen peroxide (H2O2), more effectively than either Trolox or vitamin C. Collectively our results demonstrate that indicaxanthin can be

incorporated into the redox machinery of beta-thalassemic RBC and defend the cell from oxidation, possibly interfering with perferryl-Hb, a reactive intermediate in the hydroperoxide-dependent Hb degradation. Opportunities of therapeutic interest for beta-thalassemia may be considered.

**What are the possible side effects of Indicaxanthin**

In a study on heart disease conducted at the Houston Institute for Clinical Research, the power of beets to promote nitric oxide (NO) production was shown to curb cardiovascular risk factors.

**Vitamins used in Thalassemia**

These agents are compounds that are present in small amounts in food and are essential for normal metabolism, cell function, and healthy tissues.

**Ascorbic acid (Cecon, Cevalin, Vita-C)**

Vitamin C has been shown to enhance the function of deferoxamine by keeping iron in a form that can be chelated. When administered with deferoxamine, allows more iron to be removed.

**Dosage:**

***Adult***

100-200 mg/d PO during deferoxamine therapy

***Pediatric***

3 mg/kg/d PO with SC deferoxamine infusion

**Interactions**:

Decreases effects of warfarin and fluphenazine; increases aspirin leve

**Contraindications:**

Documented hypersensitivity

**Precautions:**

***Pregnancy***

A - Fetal risk not revealed in controlled studies in humans

***Precautions***

Use in patients with severe iron overload may induce a short-term deterioration with acute cardiac toxicity

**Folic acid (Folvite)**

Required for DNA synthesis; therefore, patients with all conditions associated with rapid cellular turnover, such as hyperactive marrow in thalassemia, have greatly increased demand. Because use of folic acid in hemolytic anemias is extreme, deficiency states are fairly common in most of these patients. Patients who do not receive folic acid supplementation may develop megaloblastic anemia, increasing the severity of the original disease process.

**Dosage:**

***Adult***

1 mg PO qd

***Pediatric***

Administer as in adults

**Interactions:**

Increase in seizure frequency and a decrease in subtherapeutic levels of phenytoin reported when used concurrently

**Contraindications:**

Documented hypersensitivity; pernicious anemia; aplastic anemia

**Precautions:**

***Pregnancy***

A - Fetal risk not revealed in controlled studies in humans

***Precautions***

Pregnancy category C if dose exceeds RDA; benzyl alcohol may be contained in some products as a preservative (associated with a fatal gasping syndrome in premature infants); resistance to treatment may occur in patients with alcoholism and deficiencies of other vitamins

**Vitamin E (Vita-Plus E Softgels, Vitec, Aquasol E)**

In newborn or premature infants, in particular, deficiency has resulted in peculiar red blood cell morphology, leading to hemolysis; these changes are reversed by vitamin E. Peroxidation of membrane lipids by various

oxidants, including iron-mediated oxygen radicals, is the main cause of this hemolysis and can be prevented by antioxidants such as vitamin E.

**Dosage:**

***Adult***

50-2000 IU/d PO

**Interactions:**

Mineral oil decreases absorption of vitamin E; vitamin E delays absorption of iron and increases effects of anticoagulants

**Contraindications**:

Documented hypersensitivity

**Precautions**

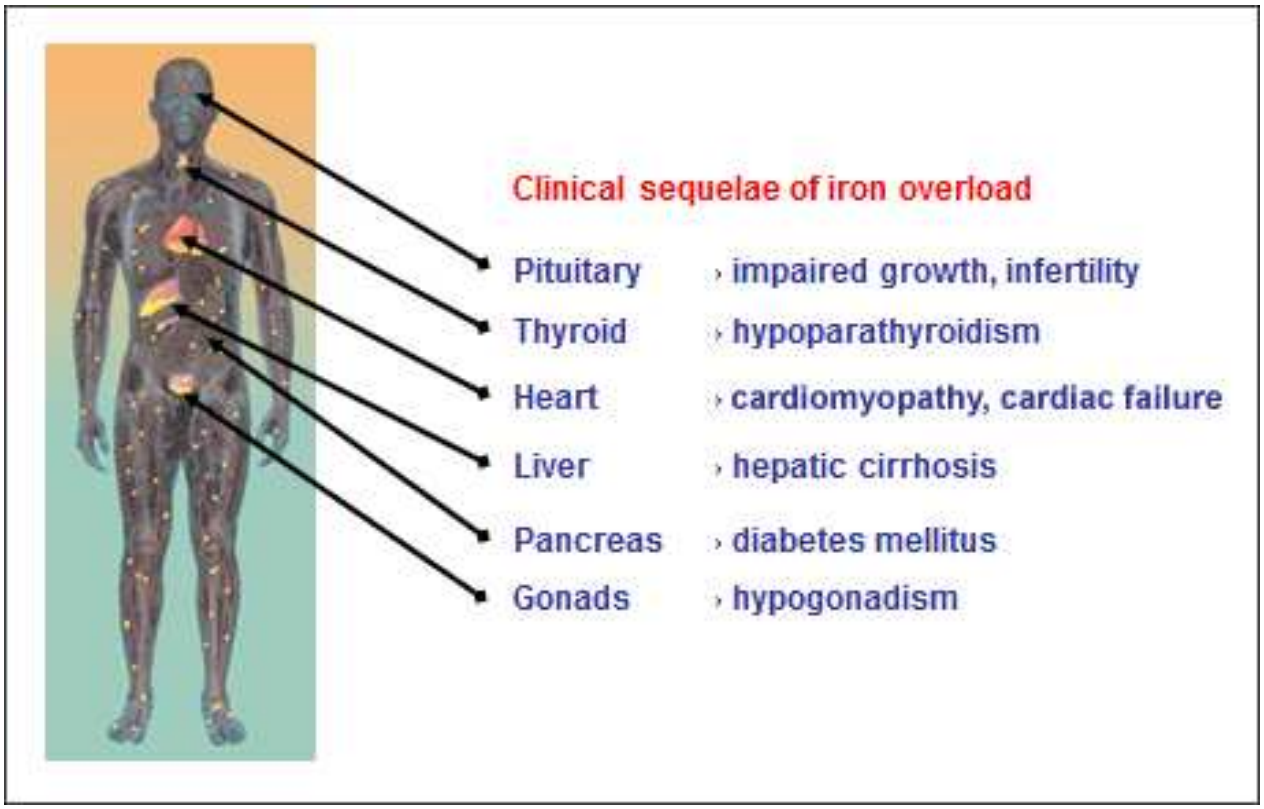
Pregnancy category C if dose exceeds RDA; vitamin E may induce vitamin K deficiency; necrotizing enterocolitis may occur when large doses of vitamin E are administered.

**Additional facts:**

Recently, increasing reports suggest that up to 5% of patients with beta-thalassemias produce fetal hemoglobin(HbF), and use of hydroxyurea also has a tendency to increase the production of HbF, by as yet unexplained mechanisms.

**Complications**

**Iron overload:** People with thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver and endocrine system, which includes glands that produce hormones that regulate processes throughout the body. The damage is characterized by excessive iron deposition. Without adequate iron chelation therapy, almost all patients with beta-thalassemia will accumulate potentially fatal iron levels.




Infection: people with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed.

Bone deformities: Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones.

Enlarged spleen: the spleen aids in fighting infection and filters unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of a large number of red blood cells, and the task of removing these cells causes the spleen to enlarge. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may necessitate its removal.

Slowed growth rates: anemia can cause a child's growth to slow. Puberty also may be delayed in children with thalassemia.

Heart problems: such as congestive heart failure and abnormal heart rhythms (arrhythmias), may be associated with severe thalassemia.

**Diet for Thalassemia:**

A well-balanced diet with adequate folic acid supply is a necessity. Foods with high iron content should be avoided, particularly meat because heme iron is especially well absorbed. Vitamin C assists absorption of dietary iron; patients should avoid co-ingesting vitamin C and iron-rich foods.

Alternatively, drinking tea with iron-rich foods helps chelate some of the iron before it is absorbed in the bowels.

**Life Expectancy Increased:**

Due to improved treatments, many patients are living longer, but longer life expectancy has led to new problems. Thalassemia patients are now struggling with secondary conditions such as heart disease, hepatitis, liver cancer, osteoporosis, and fertility problems.

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**Corresponding author:**
**Arabinda Nayak*,**
Atmiya Inst.of Pharmacy
Yogidhum Gurukul,
Kalawad Road, Rajkot,
Gujrat, India.
**Email:** *arabinda00717@gmail.com*