

Doctor.021

no. 1

HLS PHARMACOLOGY



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Modified slide no.1
V1

Drugs Used in Blood Disorders

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Pharmacology

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Reference Text Book

- Basic & Clinical Pharmacology
Bertram G. Katzung, Todd W. Vanderah

Hemato-Lymphoid System

- Agents used in Anemias and Hematopoietic growth factors: **Chapter 33**
- Drugs used in Thromboembolic Diseases: **Chapter 34**
- Drug treatment in hematopoietic malignancies: **Chapter 54**
- Antimalarial drugs: **Chapter 52**
- Antiviral drugs: **Chapter 49**

Hematopoiesis:

Requires a constant supply of:

- Essential elements:
 - Iron
 - vitamin B12
 - folic acid
- Hematopoietic Growth Factors
 - Erythropoietin
 - Myeloid Growth Factors
 - Megakaryocyte Growth Factors

Stimulate the process

Symptoms of Anemia

You should know every symptom, but focus on the highlighted ones

Red = In severe anemia

Eyes

- Yellowing

Skin

- Paleness

- Coldness

- Yellowing

Respiratory

- Shortness of breath

Muscular

- Weakness

Intestinal

- Changed stool color

Central

- Fatigue

Dizziness

- Fatigue

Blood vessels

- Low blood pressure

Heart

- Palpitations

- Rapid heart rate

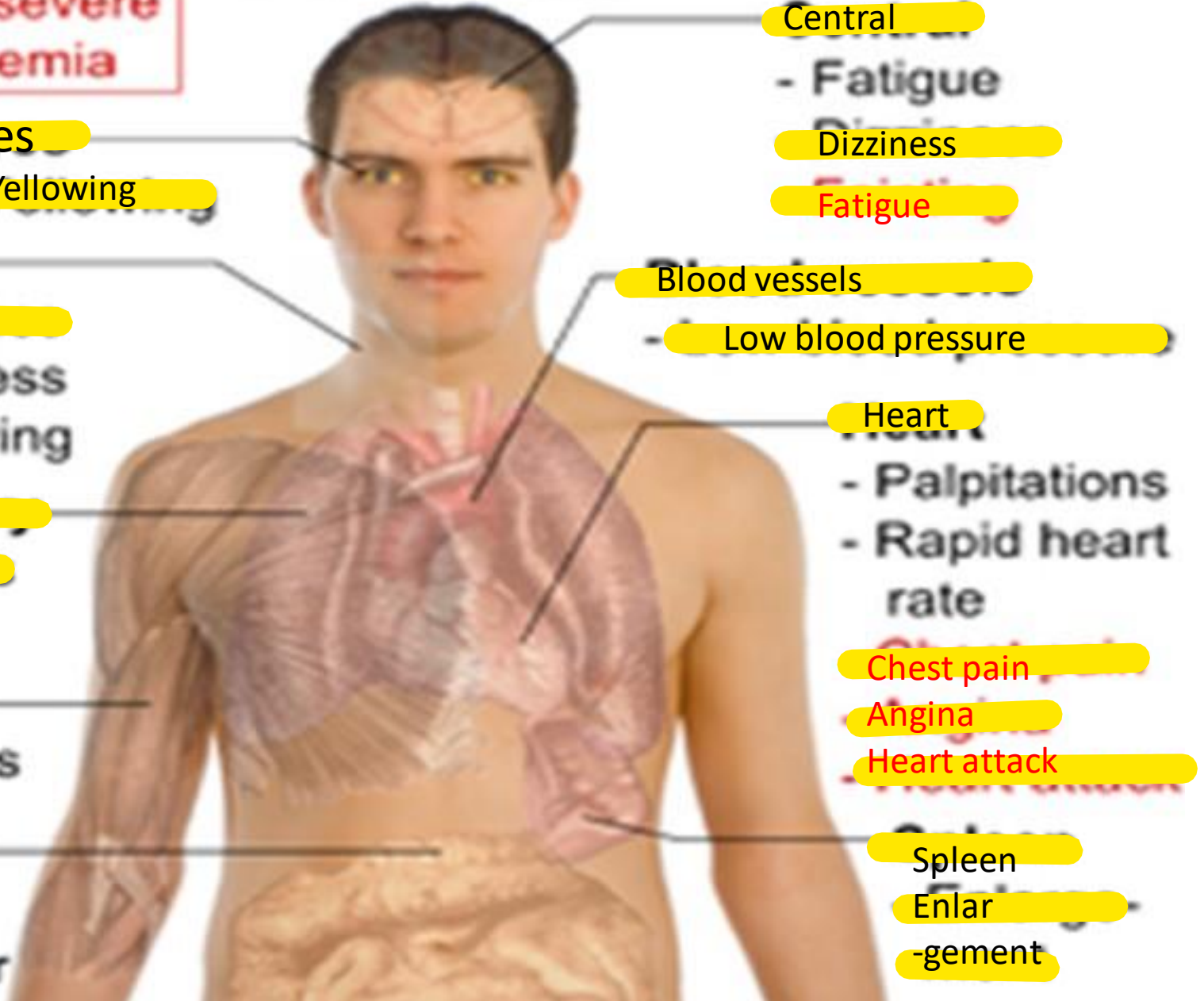
- Chest pain

- Angina

- Heart attack

Spleen

- Enlargement



Iron deficiency anemia (microcytic hypochromic anemia)

Signs:

- Pallor Blood vessels of the skin constrict, to prioritize blood to essential organs
- fatigue, dizziness
- exertional dyspnea

When we give a patient with iron deficiency anemia iron supplements it isn't going to interact with any receptor, instead it will substitute the iron inside the body

- Generalized symptoms of tissue hypoxia

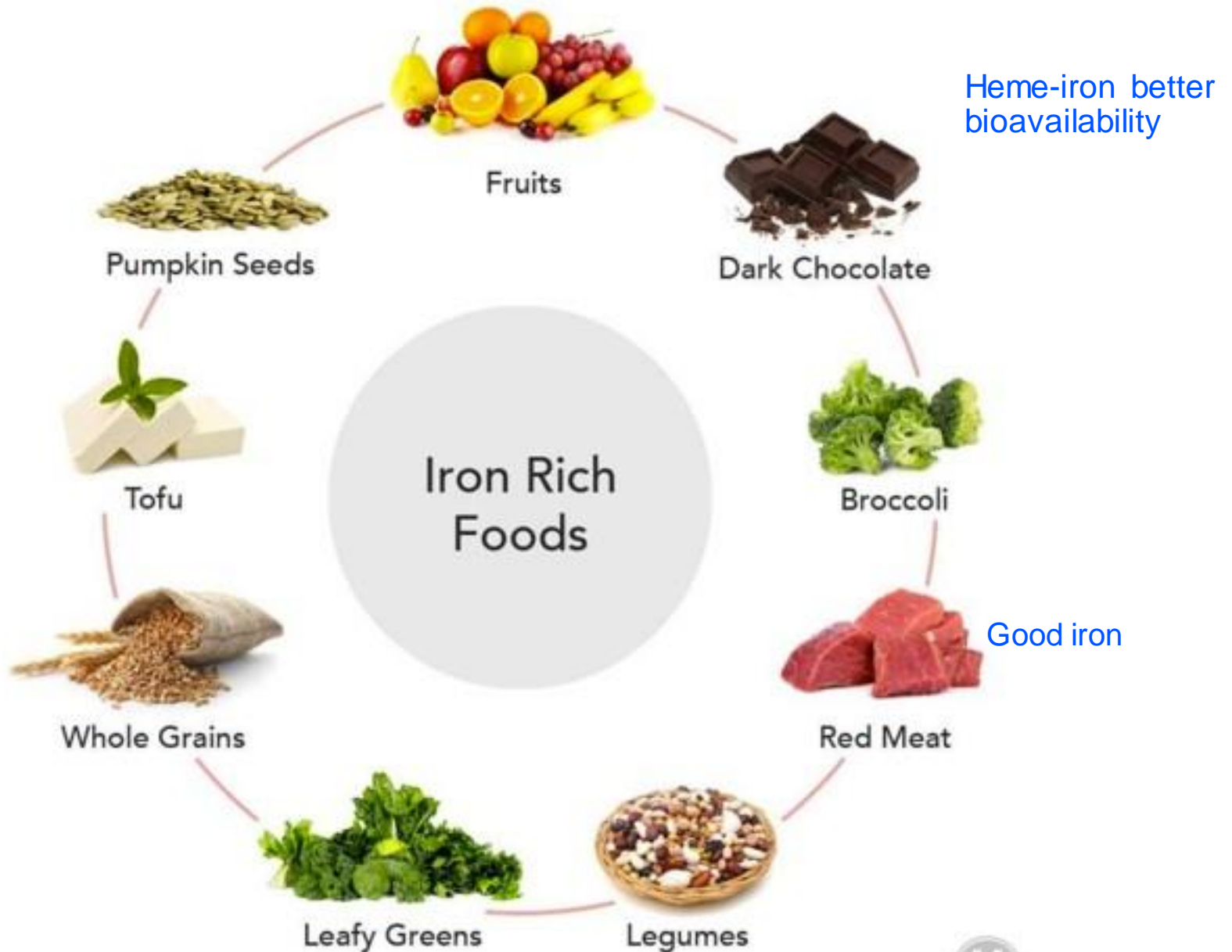
The cardiovascular adaptations to chronic anemia

- Tachycardia Low viscosity leads to low blood pressure ~> increase NO (vasodilation) through ENOS (more details in CVS next month)
- Increased cardiac output To compensate the loss
- Vasodilation.



Iron

- **Iron deficiency is the most common cause of chronic anemia - microcytic hypochromic anemia**
- **Most of the iron used to support hematopoiesis is derived from damaged RBCs.**
- **Normally small amounts are lost each day and thus, daily requirements are small.**



Iron

- Daily requirements may increase and iron deficiency may develop in certain circumstances;
 - growing children
 - pregnancy *And lactation*
 - menstruation

Iron

- **Iron content in the body in normal adults:**


You are not required to memorize this table, it is to help you compare between men and women

	Iron content (mg)	
	Men	Women
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin)	750	300
Total	4248	2314

Iron

Pharmacokinetics: Remember: ADME; absorption, distribution, metabolism, elimination.

1. Absorption:

- The average diet contains 10-15 mg of elemental iron daily.
- Normally, 5-10% of which (0.5-1 mg) is absorbed, in the duodenum and proximal jejunum.  The site of absorption
- Iron absorption increases in response to **low iron stores** or **increased iron requirements**:

Iron

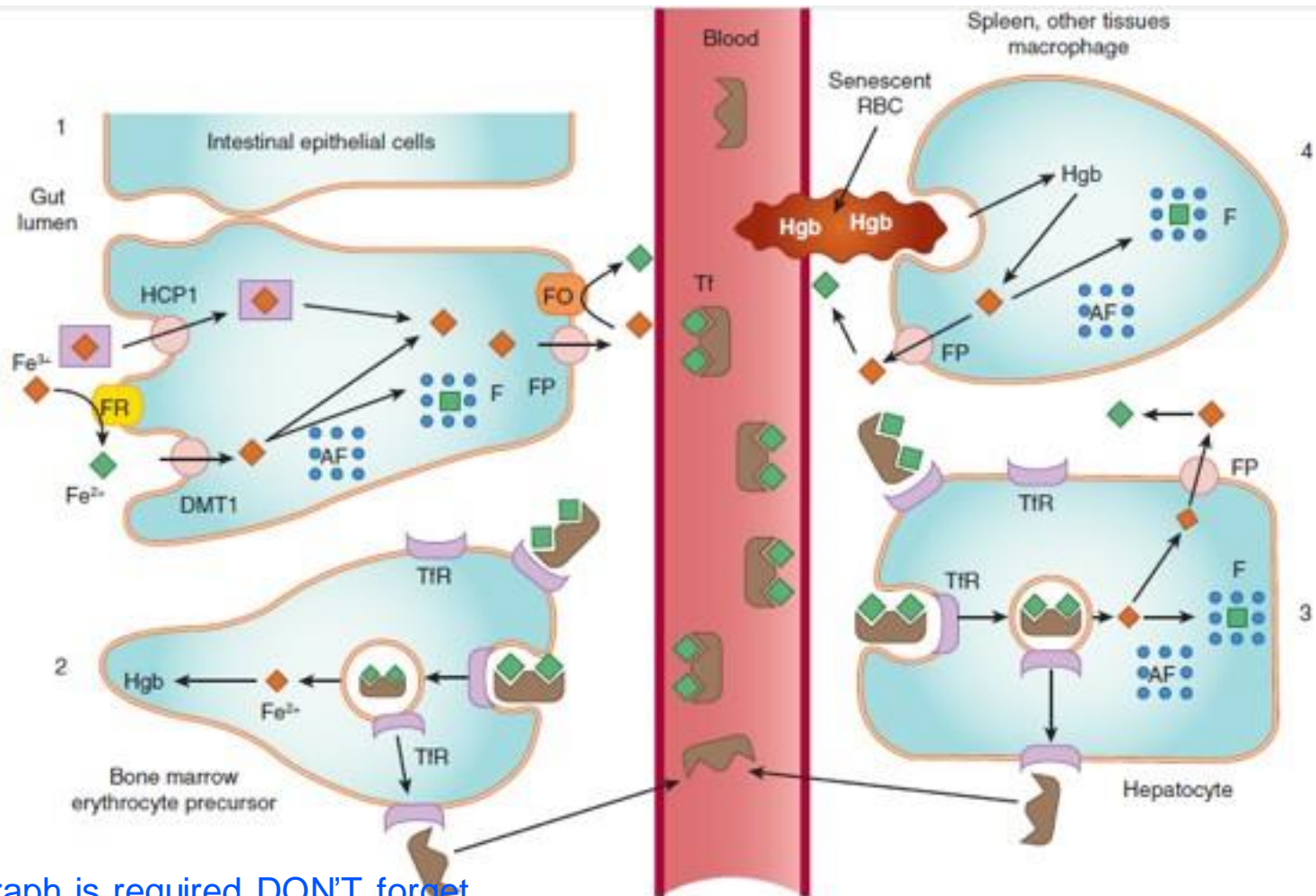
- A. **1-2 mg/day** are absorbed in **menstruating** women.
- B. **3-4 mg/day** are absorbed in **pregnant** women.
- Iron in vegetables and grains, is often tightly bound to organic compounds and is much less available for absorption.
- Iron in meat protein is efficiently absorbed, because heme iron can be absorbed intact.

Iron

- Nonheme iron in food and iron in inorganic iron salts must be reduced to ferrous iron (Fe^{2+}) to be absorbed from intestinal mucosal cells.
- Ferrous iron is transported efficiently across the luminal membrane of intestinal enterocytes **by the divalent metal transporter (DMT1).**
- Regulated by mucosal cell iron stores.

Iron

- Iron is actively transported into the blood by **ferroportin (FP)** or complexed with **apoferritin (AF)** and stored as ferritin.
- Excess iron is stored in the mucosa as **ferritin**, (a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of specialized protein called apoferritin).



This paragraph is required DON'T forget

FIGURE 33-1 Absorption, transport, and storage of iron. Intestinal epithelial cells actively absorb inorganic iron via the divalent metal transporter 1 (DMT1) and heme iron via the heme carrier protein 1 (HCP1). Iron that is absorbed or released from absorbed heme iron in the intestine (1) is actively transported into the blood by ferroportin (FP) or complexed with apoferritin (AF) and stored as ferritin (F). In the blood, iron is transported by transferrin (Tf) to erythroid precursors in the bone marrow for synthesis of hemoglobin (Hgb) (2) or to hepatocytes for storage as ferritin (3). The transferrin-iron complex binds to transferrin receptors (TfR) in erythroid precursors and hepatocytes and is internalized. After release of iron, the TfR-Tf complex is recycled to the plasma membrane and Tf is released. Macrophages that phagocytize senescent erythrocytes (RBC) reclaim the iron from the RBC hemoglobin and either export it or store it as ferritin (4). Hepatocytes use several mechanisms to take up iron and store the iron as ferritin. FO, ferrooxidase. (Modified and reproduced, with permission, from Trevor A et al: *Pharmacology Examination & Board Review*, 9th ed. McGraw-Hill, 2010.)

Iron

2. Transport:

- Iron is transported in the plasma bound to transferrin.
- The transferrin-iron complex enters maturing erythroid cells by **transferrin receptor-mediated endocytosis**.

Iron

- **The iron released in endosomes is used for hemoglobin synthesis, whereas the transferrin-transferrin receptor complex is recycled to the plasma membrane, where the transferrin dissociates and returns to plasma.**
- **Increased erythropoiesis is associated with increased number of transferrin receptors.**
- **Iron store depletion and iron deficiency are associated with increased serum transferrin.**

Iron

3. Storage:

- Iron is stored as ferritin in macrophages in the liver, spleen, bone, and in parenchymal liver cells.
- Ferritin is proportionately detected in serum.

Ferritin in plasma is in equilibrium with Ferritin in tissue

Iron

4. Elimination:

- No mechanism for iron excretion.
- Small amounts are lost by exfoliation of intestinal mucosal cells.
- Thus, regulation of iron balance is achieved by changing absorption and storage.

Iron

Clinical Pharmacology:

A. Indications:

- The only indication is treatment or prevention of iron deficiency anemia.
- **It is seen in populations with:**
 1. **Increased iron requirements:**
 - a. Infants, especially premature.
 - b. Children during rapid growth episodes.
 - c. Pregnant and lactating women.

Iron

2. Increased iron loss:

a. Chronic kidney disease - loss of RBCs during hemodialysis

b. Blood loss - most common in adults

- Menstruation (~ 30mg/cycle)

- Upper gastrointestinal bleeding Severe peptic ulcers

Iron

3. Inadequate iron absorption:

a. **Gastrectomy (?)** Decrease in acid ~> decrease in iron absorption

Absorption (acidity accelerate the reduction of Fe⁺³ into Fe⁺²)

b. **Severe small bowel disease -
generalized malabsorption.**

Iron

B. Treatment:

1. Oral Ferrous Iron Salts:

Elemental iron per tablet	Tablet size (mg)	Preparation
65	325	Ferrous sulfate hydrated
36	325	Ferrous
106	325	Ferrous

Iron

- In an iron-deficient individual, ~ 50-100 mg of iron can be incorporated into hemoglobin daily, **and about 25% of iron given as ferrous sulfate can be absorbed.**
- Therefore, 200- 400 mg of elemental iron should be given daily for 3-6 months **after correction of the cause of the iron deficiency anemia, to correct the anemia and replenish iron stores.**

Iron

Oral Iron Preparations:

- Ferrous sulfate.
- Ferrous gluconate.
- Ferrous fumarate.
 - All are effective and inexpensive.

Iron

Adverse effects:

1. Nausea, epigastric discomfort, abdominal pain, constipation and diarrhea. Mostly constipation
- These effects are dose-related and can be reduced by lowering the dose or giving it with meals or immediately after meals.
2. Black stools are common and may obscure the diagnosis of continued gastrointestinal blood loss.