IRON CHELATING AGENT

Dr. Farida Parvin
Assistant Professor
Transfusion Medicine & Clinical Hematology Department
BIRDEM General Hospital

DEFERASIROX

A GOLD STANDARD

CHELATOR

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Introduction

- It is the first oral medication approved in the USA for iron chelation.
- It was approved by the United States Food and Drug Administration (FDA) in November 2005.
- Has been licensed as first-line monotherapy for thalassaemia major in over 100 countries worldwide.

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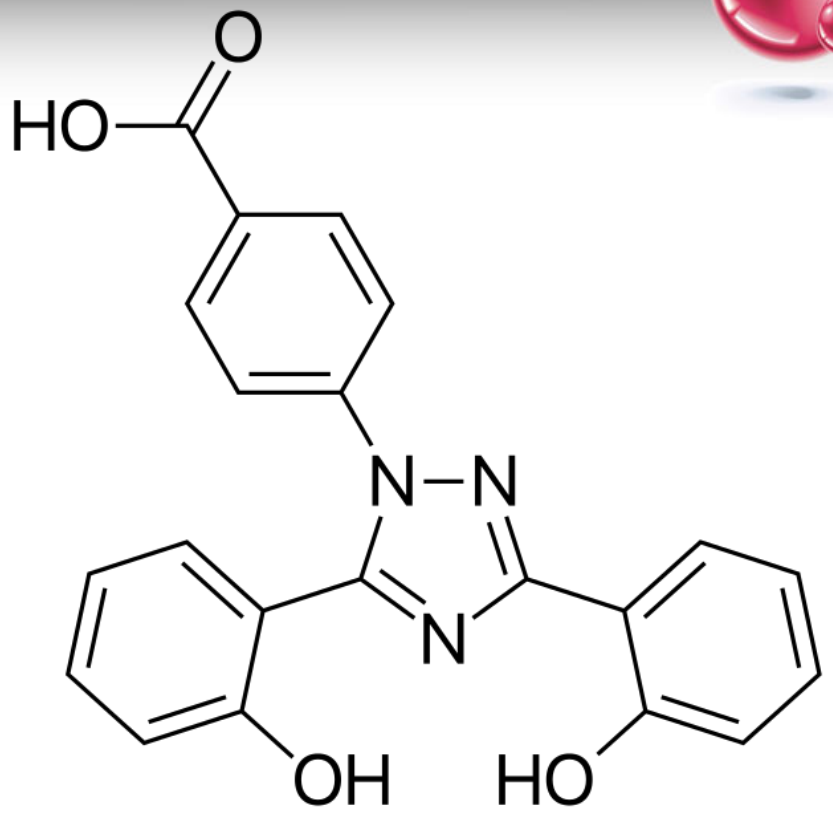
Deferasirox Data

- Deferasirox is an orally absorbed tridentate iron chelator.
- Bioavailbility:70%
- Protein binding:99%
- Metabolism: Hepatic glucoronidation.
- Biological half life :8 to 16 hours.



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Deferasirox Data cont….

- Peak plasma concentrations occur within 1-2 hours of administration.
- Excretion: Fecal (84%) and renal(8%).
- This relatively long elimination facilitates once daily dosing.

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Chemistry and Pharmacology

- Two molecules of Deferasirox are capable of binding to 1 atom of iron (2:1 complexes).
- Its low molecular weight and high lipophilicity allows the drug to be taken orally unlike DFO which has to be administered by IV route (intravenous infusion).

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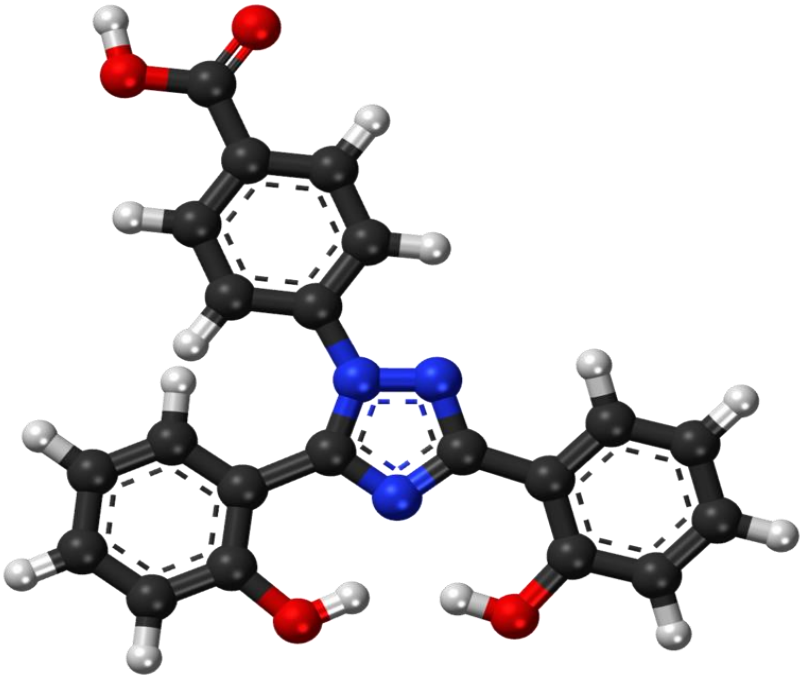
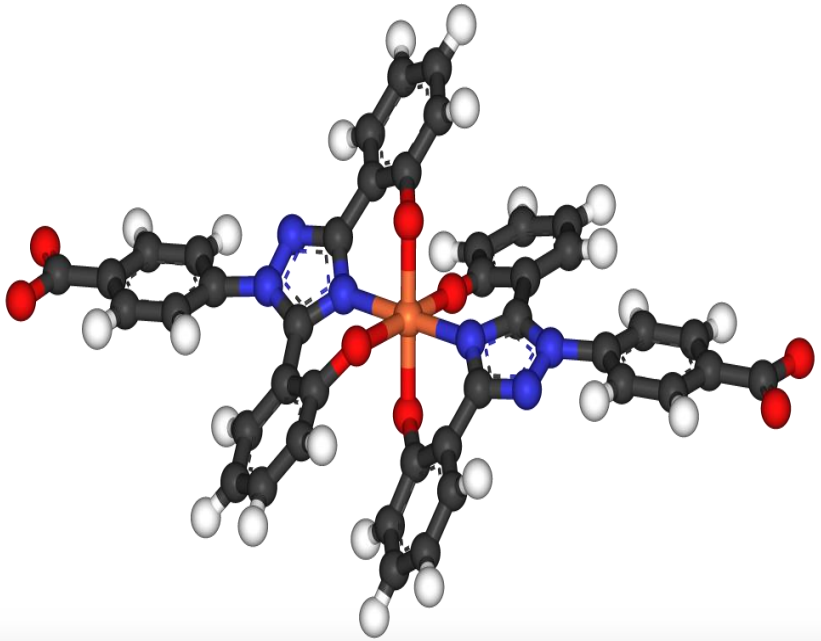
Chemistry and Pharmacology cont….

Deferasirox



2 DFX molecules binding iron



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TIF guidelines Published by TIF in 2014

Current indications of the Deferasirox

- Treatment of chronic iron overload due to frequent blood transfusions in patients with β-thalassaemia major .
- ✓ In the United States (FDA), DFX can be used to initiate treatment in children as young as 2 years, commencing at a dose of 20 mg/kg.
- ✓ In Europe (European Medicines Evaluation Agency), DFX is only approved as a second-line drug for children younger than 6 years.

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Current indications of the Deferasirox

- When Deferoxamine therapy is contraindicated or inadequate in:

✓ patients with other anaemias

✓ patients aged 2–5 years

✓ patients with β-thalassaemia major with infrequent blood transfusions.

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Deferasirox in Pregnancy

- Should be stopped in pregnancy and during breast feeding.
- Sexually active patients receiving DFX should use contraception.
- Pregnancy Category - C

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Deferasirox in NTDT

- DFX is both safe and efficacious in NTDT patients.

- Early dose escalation of DFX is effective in more heavily iron-overloaded patients with non-transfusion-dependent anaemias.

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Dosage OF Deferasirox

- Recommended starting dose 20mg/kg
- To maintain iron balance give 10mg-20mg/kg
- To reduce iron burden 30mg/kg

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Dose adjustment

- Dose adjustment must be based on the results of monitoring .
- Made in 5-10mg/kg steps to fit both the patient's response and therapeutic goals.
- In adults the daily dose can be reduced by 10mg/kg if serum creatinine rises >33% above pre-treatment measurements on 2 consecutive visits and no other cause can be found.

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Administration of Deferasirox

- Deferasirox should be taken on an empty stomach at least 30 min. before meals preferably morning at the same time daily and not with any antacids.
- It is administered orally as a tablet that is dissolved in 100-200mL of water. (It must not be dissolved in fizzy drinks).

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Tablets come in 100mg,250mg, 400mg,500 mg doses

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Monitoring of patient

	Test required
Before starting Deferasirox	Serum ferritin Serum creatinine Creatinine clearance Liver function tests
1st month of treatment	Serum creatinine (weekly) Creatinine clearance (weekly)

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Monitoring cont…

	Test required
After Dose adjustment	Serum creatinine Creatinine clearance
Monthly	Serum creatinine Creatinine clearance Liver function tests
Monthly (In transfused patients) **3 monthly in untransfused**	Serum Ferritin
Yearly	Audiometry and Ophthalmic review

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Side effects of Deferasirox

	Side effect	Action
Common	Rise in creatinine Elevated liver enzymes Headache Abdominal distension Proteinuria	**dose adjustment**
Rare	Anxiety, dizziness, early cataract, hearing loss, gastritis, hepatitis, pigmentation disorder,rash, pyrexia, fatigue, oedema, glycosuria.	

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Deferasirox : safety profile

Adverse event	Frequency (% patients)	Observations
Non-progressive increase in serum creatinine	36	Mild, mostly within normal range; dose dependent,often resolve spontaneously; may be sometimes alleviated by dose reduction.
Gastrointestinal disturbance (nausea, vomiting, diarrhoea , abdominal pain)	26	Dose-dependent, mostly mild to moderate, generally transient and self-limiting even with continued therapy.
Skin rash	7	Dose-dependent, mostly mild to moderate, generally transient and self-limiting with continued therapy.
Elevation in liver transaminases	2	Most patients had elevated levels prior to deferasirox treatment Elevations > 10 x upper limit of normal (ULN) were uncommon (0.3%)
High-frequency hearing loss and lenticular opacities	≤ 1	Uncommonly observed with patients taking deferasirox

Contraindication of Deferasirox

- serum creatinine >2 times the age-appropriate upper limit of normal.
- Estimated creatinine clearance <60 ml/min
- Hepatic impairment.
- Hypersensitivity to the active substance .

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Advantages of Deferasirox

- Orally active with long plasma half-life.
- Generally well tolerated over a range of transfusion-dependent anaemias.
- Once-daily and Ease of administration.
- 24-h chelation and increased chelation efficiency.
- Clear dose response effect on iron balance.
- No reported adverse effect on children's growth or on adolescent sexual development

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Advantages of Deferasirox cont.…

- Capable of removing iron from cells (cardiac myocytes and hepatocytes) as well as removing iron from the blood.
- No drug-induced agranulocytosis, neutropaenia, or arthralgia .
- Licensed as first-line treatment in iron overload.
- Demonstrated equivalency to DFO at higher doses.

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Disadvantages of Deferasirox

- Need to monitor renal function.
- Not all patients achieve negative iron balance at highest recommended dose.
- Contraindicated in pregnancy.

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Challenges of Deferasirox

- Cost , especially with higher doses

AND

- Gastrointestinal side effects may limit optimal dosing.

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Maintenance therapy

- Maintenance therapy is adjusted to prevent tissue damage because of iron overload.
- Serum ferritin 2500 ng/ml indicate inadequate chelation.
- All patients may not be satisfactorily chelated on DFO, DFP, or DFX alone.
- The patient switched to another chelator or switched to combined therapy.

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Combined therapy : DFX and DFO

- DFX 20-30mg/kg daily combined with DFO 35-50mg/kg S/C on 3-7 days each weak.
- Liver iron improved significantly.
- No excessive toxicity effect.

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Combined therapy: DFP and DFX

- DFP 75-100 mg/kg per day in 3 divided doses together with DFX 20-25 mg/kg each day.
- Fall in total body iron .
- Compliance is excellent.
- Quality of life will be improved .
- Improvement in cardiac iron with cardiac function .
- No unexpected side effects.

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Sequential therapy : DFX and DFO

ATTRACTIVE OPTION

- DFX for 4 consecutive days (20-30 mg/kg per day)& DFO for 8-12 hours on the next 3 consecutive days (20- 40 mg/kg per day).
- Decrease in serum ferritin without any side effects.

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SO…… Iron chelation must be

TAILORED

- Reduction of body iron and maintenance of body iron Should be balanced according to iron intake and pre-existing iron load.

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Challenging task for the future

FOR DESIGNING A CHELATOR

- Is orally active
- Can cross cell membranes
- Is capable of scavenging iron from specific areas of the body, such as the heart, the liver, the endocrine glands and the brain, sparing the bulk of physiologically essential iron.

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Newer Iron Chelator

- Desferrithiocin
- Hydroxy Benzyl Ethilene Diamine Diacetic acid (HBED)
- Pyridoxal iso nicotinyl Hydrazone (PIH)
- GT 56-252
- 40 SD02 (CHF 1540)

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Conclusion

- Ease of administration, ensuring compliance, is an important property in choosing an iron chelator.
- The cost and availability of oral iron chelators is an important issue for patients.
- Adherence may also be improved by offering patients greater choice in chelation.
- Encouraging a patient to take control or self manage is often a useful approach of long term benefit.

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Thank You

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