Approved Medicines in Sickle Cell Disease and Thalassemia Diseases and Regulatory Considerations by FDA CDER

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CDER Approvals

- **Small molecule drugs and some biologics**
  - Monoclonal antibodies, immune modulator
- **Demonstrate positive benefit: risk assessment**
  - Safety: data from sufficient number of patients with the condition, exposed to the drug for long enough and show that the drug is reasonably safe in the context of its benefits
  - Benefit:
    - Establish substantial evidence of effectiveness based on
      - 2 adequate and well controlled trials, or
      - 1 adequate and well controlled trial that is the equivalent of 2 trials, or
      - 1 adequate and well controlled trial plus confirmatory evidence
    - For traditional approval must demonstrate improvement on clinically meaningful endpoint (how patient feels, functions, survives) or validated surrogate endpoint

Drug Approvals in Thalassemia in CDER

- **Iron Chelators**
  - Deferasirox
  - Deferoxamine

- **Ameliorate ineffective hematopoiesis**
  - Luspatercept

Exjade (Deferasirox) Approval on November 2, 2005

- Iron chelating agent indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older.
- Approval based on 3 Studies:
  - **Study 1:** Multicenter, open-label, randomized, active comparator control study comparing Exjade to deferoxamine.
    - Patients >= 2 years of age with β-thalassemia and transfusional hemosiderosis.
    - In patients who had liver iron concentration (LIC) at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with Exjade and -2.9 mg Fe/g dry weight in patients treated with deferoxamine. Reduction of LIC and serum ferritin was observed with Exjade doses of 20 to 30 mg/kg per day.
  - **Study 2:** Open-label, single arm study of Exjade given to patients with chronic anemias and transfusional hemosiderosis.
    - 184 patients treated including 85 patients with β-thalassemia
    - Reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).
  - **Study 3:** Multicenter, open-label, randomized trial of Exjade compared to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis.
    - 195 patients were treated in this study
    - Mean change in LIC was -1.3 mg Fe/g dry weight for patients receiving Exjade (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

Reblozyl® (Luspatercept)

- Erythroid maturation agent indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusion.
- Efficacy was established in adults with beta thalassemia in the BELIEVE trial
  - Multicenter, randomized, double-blind, placebo-controlled trial
  - 336 patients with beta thalassemia requiring regular red blood cell transfusions
  - Patients allowed to receive best supportive care (included RBC transfusions; iron-chelating agents)
  - Efficacy established based upon the proportion of patients achieving RBC transfusion burden reduction (≥33% reduction from baseline) with a reduction of at least 2 units from Week 13 to Week 24.

	Reblozyl	Placebo	Risk Difference	P-value
Week 13 to Week 24	47 (21.0)	5 (4.5)	16.5 (9.9, 23.1)	<0.0001
Week 37 to Week 48	44 (19.6)	4 (3.6)	16.1 (9.8, 22.4)	<0.0001

Drug Approvals in Sickle Cell Disease in CDER

- Deferiprone
- Hydroxyurea (Droxia®, Siklos® and Xromi®)
- L-Glutamine
- Crizanlizumab-tmca
- Voxelotor

Oxbryta® (Voxelotor)

- Granted accelerated approval
- Hope trial: Phase 3 randomized, double-blind, placebo-controlled, multicenter trial
  - 274 patients (12 to 65 years of age) randomized to receive OXBRYTA 1,500 mg (N=90), OXBRYTA 900 mg (N=92), or placebo (N=92)
  - Enrolled patients with 1 to 10 vasoocclusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL.

Oxbryta® (Voxelotor)

- Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy on study
- Efficacy was based on Hb response rate defined as a Hb increase of >1 g/dL from baseline to Week 24 in patients treated with OXBRYTA 1,500 mg versus placebo.
- Response rate for OXBRYTA 1,500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$).

THANK YOU


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