TEXAS Health and Human Services

Medicaid Drug Use Criteria

Sickle Cell Disease Products

- Developed April 2020

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Current therapeutic options available for the outpatient management of sickle cell disease include hydroxyurea (Droxia®, Siklos®), L-glutamine (Endari®), and voxelotor (Oxbryta®). Hydroxyurea is a chemotherapeutic agent used to stimulate red blood cell (RBC) fetal hemoglobin (HbF) production, which is associated with a lower risk of acute sickle cell complications. Although the exact mechanism of action for sickle cell disease is unknown, hydroxyurea is FDA approved for patients with recurrent moderate-to-severe painful crises to reduce the frequency of painful

crises and the need for blood transfusions. However, hydroxyurea cannot be used to treat crises.[1-7] L-glutamine is an essential amino acid thought to decrease oxidative damage to sickled RBCs by increasing nicotinamide adenine dinucleotide (NAD^+) synthesis, thereby reducing the acute complications of sickle cell disease such as chronic hemolysis and vaso-occlusive events.[1-5,8] Voxelotor is a first-in-class hemoglobin S (HbS) polymerization inhibitor which increases the affinity of HbS for oxygen by stabilizing the oxygenated hemoglobin state.[2-5,9]

Maximum recommended adult dosages are summarized in Table 1. Medication profiles identifying patients prescribed dosages exceeding these recommendations will be reviewed.

Table 1: Maximum Daily Adult Dosages for Sickle Cell Disease Products[1-9]

Drug Name	Dosage Form / Strength	Treatment Indication	Maximum Recommended Dosage
Hydroxyurea (Droxia®)	200 mg, 300 mg, 400 mg capsules	Reduction in frequency of painful crises and to reduce the need for blood transfusions in patients with moderate to severe painful crises	35 mg/kg/day as long as blood counts are within acceptable range
Hydroxyurea (Siklos®)	100 mg, 1000 mg tablets	Reduction in frequency of painful crises and to reduce the need for blood transfusions in patients with moderate to severe painful crises	35 mg/kg/day as long as blood counts are within acceptable range
L-glutamine (Endari®)	5 gram powder packets	Reduction in acute complications of sickle cell disease	Based on patient weight: Less than 30 kg 5 g twice daily 30-65 kg 10 g twice daily Greater than 65 kb 15 g twice daily
Voxelotor (Oxbryta®)	500 mg tablets	Treatment of sickle cell disease	1500 mg once daily+

- + voxelotor dose should be increased to 2500 mg once daily if prescribed concurrently with moderate/strong CYP3A4 inducers or reduced to 1000 mg once daily in patients with severe hepatic impairment

1.2 Pediatrics

L-glutamine (Endari®), voxelotor (Oxybryta®), and hydroxyurea as Siklos® have been approved for use in pediatric patients, but the safety and efficacy of

hydroxyurea as Droxia® has not been established in pediatric patients.[6-10] Hydroxyurea (Siklos®) is approved for patients 2 years of age and older to reduce the frequency of recurrent moderate-to-severe painful crises. Growth should be continuously monitored in pediatric patients prescribed hydroxyurea; additionally, pediatric patients 2-16 years of age are at greater risk of developing neutropenia compared to patients older than 16 years.[7] L-glutamine is approved for pediatric patients 5 years and older, while voxelotor® is approved for patients 12 years of age based on clinical trials which demonstrated similar safety and efficacy outcomes to adult patients.[2,8,9]

The maximum recommended pediatric dose for individual agents is summarized in Table 2. Prescribed dosages exceeding these recommendations will be reviewed.

Table 2: Maximum Daily Pediatric Dosages for Sickle Cell Disease Products[1-10]

Drug Name	Dosage Form / Strength	Treatment Indication	Maximum Recommended Dosage
Hydroxyurea (Siklos®)	100 mg, 1000 mg tablets	Reduction in frequency of painful crises and to reduce the need for blood transfusions in patients with moderate to severe painful crises	2-18 years of age: 35 mg/kg/day as long as blood counts are within acceptable range
L-glutamine (Endari®)	5 gram powder packets	Reduction in acute complications of sickle cell disease	Based on patient weight: Less than 30 kg 5 g twice daily 30-65 kg 10 g twice daily Greater than 65 kb 15 g twice daily
Voxelotor (Oxbryta®)	500 mg tablets	Treatment of sickle cell disease	1500 mg once daily+

- +voxelotor dose should be increased to 2500 mg once daily if prescribed concurrently with moderate/strong CYP3A4 inducers or reduced to 1000 mg once daily in patients with severe hepatic impairment

2 Duration of Therapy

There is no basis for limiting long-term therapy of sickle cell disease; however, treatment with hydroxyurea requires monitoring of blood counts every 2 weeks due to the risk of myelosuppression. Hydroxyurea should be discontinued until hematologic recovery if blood counts reach toxic ranges defined as: neutrophils less

than 2,000/mm^3, platelets less than 80,000/mm^3, hemoglobin less than 4.5 g/dL, or reticulocytes less than 80,000/mm^3 if hemoglobin is less than 9 g/dL.[2,5-9]

3 Duplicative Therapy

Sickle cell disease treatment is complex and may require combination therapy. Both L-glutamine and voxelotor can be used alone or in combination with hydroxyurea. In a phase 3 clinical trial, investigators found L-glutamine was effective in preventing vaso-occlusive pain in patients with frequent episodes (≥2 in the prior year), regardless of hydroxyurea use; therefore, it can serve as an alternative to hydroxyurea or be used as an adjunctive therapy.[5,11] Similarly, voxelotor may be administered with or without hydroxyurea to reduce sickle cell anemia.[2,4,9,12] There is currently no evidence to support the concurrent use of L-glutamine and voxelotor to manage sickle cell disease.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Major drug-drug interactions considered clinically significant for sickle cell disease products are summarized in Table 3. Only those drug-drug interactions classified as clinical significance level 1/contraindicated or those considered life-threatening which have not yet been classified will be reviewed.

Table 3. Sickle Cell Disease Product Drug-Drug Interactions[2,3,6-9]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
Hydroxyurea (Droxia®, Siklos®)	Live Vaccines (MMR*, Varicella, Zoster, Smallpox, Typhoid, Yellow fever, Rotavirus+)	May increase risk of infection by live vaccine	Avoid use until at least 3 months after discontinuation of immunosuppressive drugs unless benefits clearly outweigh potential risks	Contraindicated (DrugReax) 1 – severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
Hydroxyurea (Droxia®, Siklos®)	Stavudine	May increase risk of severe peripheral neuropathy, fatal pancreatitis, and hepatotoxicity	Avoid concurrent use	Major (DrugReax) 2 – major (CP)
Hydroxyurea (Droxia®, Siklos®)	Didanosine	May result in fatal pancreatitis and hepatotoxicity	Avoid concurrent use	Major (DrugReax) 2 – major (CP)
Voxelotor (Oxbryta®)	Strong or moderate CYP3A4 inducers (e.g. phenytoin, nafcillin, carbamazepine)	May reduce voxelotor plasma concentration and result in reduced efficacy	Avoid concurrent use or increase voxelotor dosage to 2500 mg daily	Major (DrugReax) 2 – major (CP)
Voxelotor (Oxbryta®)	Fluconazole	May increase voxelotor plasma concentration and result in increased toxicity	Avoid concurrent use, replace with alternative drugs, or decrease voxelotor dosage to 1000 mg daily	Major (DrugReax) 2 – major (CP)
Voxelotor (Oxbryta®)	Strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole)	May increase voxelotor plasma concentration and result in increased toxicity	Avoid concurrent use, replace with alternative drug, or Decrease voxelotor dosage to 1000 mg daily	Major (DrugReax) 2 – major (CP)
Voxelotor (Oxbryta®)	CYP 3A4 substrates with narrow therapeutic indices (e.g. oxycodone, cyclosporine, fentanyl, tacrolimus)	May result in increased concentration of sensitive CYP3A4 substrates	Avoid concurrent use or consider dose reduction of sensitive CYP3A4 substrates	Major (DrugReax) 3 – moderate (CP)

- *MMR-Measles, mumps, rubella
- +Rotavirus vaccination is indicated up to 24 months of age; because hydroxyurea (Siklos®) is indicated for use in pediatric patients 2 years and older, there is a small chance that a patient might be considered for both treatments; this combination should be avoided.

5 References

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