Maryland
DEPARTMENT OF HEALTH

PHARMACY
News & Views

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Responsible Use of Prospective DUR Intervention Codes

A prospective drug utilization review (ProDUR) is performed electronically on every claim submitted to the Maryland Medicaid Pharmacy Program (MMPP). ProDUR alerts are returned with the claim and are used to identify conflicts in drug therapy such as therapeutic duplication, drug-drug interactions, refills too soon, and high doses.

In a recent review of override codes for the ProDUR alerts, it was found that M0 was mostly utilized which indicated that the prescriber was consulted. The MMPP relies on the pharmacist to use their best clinical judgment to determine when the prescriber should be consulted. The M0 code is applied when the prescriber has been consulted and has indicated that the alerted therapy conflict is part of the intended course of treatment for the patient. After initial documentation of discussion with the prescriber, the prescriber should be contacted again after a reasonable period of time, such as six months, to determine if the therapy conflict should continue. Pharmacists must also document all interventions and communications on the prescription hardcopy for auditing purposes.

INTERVENTION CODES		OUTCOME CODES	
M0 *	Prescriber consulted	1A	Filled as is, false positive
R0 *	Pharmacist consulted	1B	Filled prescription as is
P0 *	Patient consulted	1C	Filled with different dose
* second digit is zero, not letter "O"		1D	Filled with different directions
		1E	Filled with different drug
		1F	Filled with different quantity
		1G	Filled, prescriber approval

Hemoglobin-impacting Genetic Disorders

Sickle cell disease (SCD) and thalassemia are genetic disorders impacting hemoglobin. In SCD, the red blood cells (RBC) are rigid and "C", or sickle, shaped. While thalassemia impacts the number of RBC.

Sickle Cell Disease

SCD is the most common genetic blood disorder, impacting 100,000 Americans. It is most prevalent in people descending from Africa, Central and Southern America, the Middle East, Asia, and the Mediterranean.

SCD is caused by mutations of beta-globin gene alleles with involvement of one or more sickle mutations. Sickle cell mutations decrease the solubility of hemoglobin, making them more rigid and giving them the sickle shape.

Patients can have multiple different mutations: both sickle mutations (HbSS), one sickle mutation and one hemoglobin C mutation (HbSC), one sickle mutation and one thalassemia mutation (HbS), or other mutations with sickle mutations in the beta-globin genes.

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PAYING WITH CASH?

Medicaid participants may ask to pay cash for prescriptions of controlled substances when Medicaid has denied the claim because a participant is locked into a specific pharmacy, the refill is too soon, and/or a therapeutic duplication exists. Medicaid patients SHOULD NOT be paying cash for any prescriptions under normal circumstances. This especially applies to prescriptions for controlled substances. For more information, please visit: https://health.maryland.gov/mmcp/pap/docs/ADVISORIES/Advisory%20094.pdf

Hemoglobin-impacting Genetic Disorders *(continued)*

Symptoms of SCD are often divided into acute and chronic manifestations, although there is much overlap between the two. Acute symptoms include anemia, fatigue, jaundice, risk of infection, and vaso-occlusive symptoms including severe pain. Chronic complications can include chronic pain, anemia, neurologic deficits, pulmonary conditions, hypertension, impaired kidney function, osteoporosis, cardiomyopathy, and other conditions from recurring vaso-occlusive events.

Complications from SCD can lead to increased hospitalizations and can impact morbidity and mortality.

Thalassemia

Thalassemia is another genetic disorder in which the body makes abnormal or inadequate amounts of hemoglobin. It affects a smaller percentage of patients compared to SCD. Worldwide, 4.4 out of every 10,000 live births is affected by thalassemia trait, with at least 1,500 people with transfusion-dependent thalassemia (TDT) in the United States. Thalassemia is more common in people of Southeast Asian, South Asian, Middle Eastern, African, and Mediterranean decent.

Patients with thalassemia have reduced or absent production of one or more globin chains. Thalassemia is classified based on the type of genetic deficit causing the disease, the severity of symptoms, and the need for blood transfusions. Patients with thalassemia minor, thalassemia trait, or silent carriers typically do not experience symptoms and do not require treatment, however they are genetic carriers of the disease.

In patients with non-transfusion dependent thalassemia, one or both beta-globin genes are not functioning properly. These patients may experience mild to moderate anemia but do not required regular transfusions.

The smallest percentage of patients have transfusion-dependent thalassemia, or thalassemia major. Thalassemia is further divided into alpha and beta thalassemia. Beta thalassemia is caused by mutations in the beta globin (HBB) gene that leads to impaired production of beta globin chains, resulting in excess of alpha or alpha-type chains. Alpha thalassemia is caused by variation in the alpha globin (HBA) gene, leading to impaired production of alpha globin chains, and resulting in excess beta or beta-like chains.

Thalassemia can lead to symptoms such as jaundice, impaired growth, bone deformities, hepatosplenomegaly, iron overload with organ damage, VTE, and pathologic fractures.

Treatment

Hydroxyurea is the mainstay of treatment for patients with SCD. Data has shown that it can reduce the incidence and frequency of vaso-occlusive episodes, increase hemoglobin, reduce hospitalizations, and improve survival. However, some patients cannot tolerate hydroxyurea or do not experience reduction or alleviation of vaso-occlusive episodes with proper use. Newer therapies, including Endari or Oxbryta, can be used alone or in addition to hydroxyurea. Endari is shown to reduce painful vaso-occlusive episodes in patients with SCD and Oxbryta can increase hemoglobin levels resulting in reduction of symptoms.

Thalassemia varies in severity. Some patients require supportive therapy, while those with TDT will require transfusion every 2-5 weeks for treatment.

Currently, the only potentially curative therapy for SCD or TDT is hematopoietic stem cell transplant (HSCT). Per guidelines from the American Society of Hematology, HSCT can be considered in patients with SCD who have an overt stroke or an abnormal transcranial Doppler ultrasound, who have frequent pain, or who have recurrent episodes of acute chest syndrome. Additionally, HSCT with a human leukocyte antigen (HLA)- matched sibling donor is recommended for patients with TDT.

The FDA has recently approved gene therapies for patients with both SCD and thalassemia. Gene therapies use a process of editing a patient's own CD34* cells before returning them to the patient. This process can take a total of 7-8 months and may only be administered at authorized treatment centers. Patients must be committed to working closely with and be monitored by their treatment team throughout the process.

For more information on newly FDA approved treatments for SCD and TDT please see the table.

Table: Recent new drug approvals aim to improve the quality of life for patients with inherited red blood cell disorders.

Drug / Class	Mechanism	Cost	Indication(s)	Dosing Considerations
Adakveo (crizanlizumab) —– Monoclonal antibody	Binds P-selectin, blocking interactions between blood and endothelial cells, reducing the likelihood of occlusion	$$$	Reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease	30 minute IV administration, every 4 weeks after 2 initiation doses; Weight based dosing
Casgevy (exagamglogene autotemcel) —– Gene therapy	Patient's own $CD34^+$ cells are genetically edited to reduce expression of *BCL11A* gene, resulting in increased γ-globin expression and fetal hemoglobin protein production (HbF). This decreases the hemoglobin S (HbS) which causes sickling of red blood cells (RBCs) in SCD patients and in TDT patients γ-globin reduces the α-globin imbalance to reduce ineffective erythropoiesis and hemolysis	$$$$	Treatment of patients aged 12 years and older with: • sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) • transfusion-dependent β-thalassemia (TDT)	One time treatment; Requires myeloablative conditioning prior to infusion of modified cells; Only administered at Authorized Treatment Centers (ATCs); Total treatment time takes a minimum of 7-8 months
Endari (l-glutamine) —– Amino acid	Mechanism not fully known- believed to increase levels of pyridine nucleotides NAD+ and NADH, leading to decreased oxidative damage of RBCs	$$	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	Dose based on body weight; Powder, mixed in food or drink before ingesting; Twice daily dosing
Hydrea, Droxia, Siklos (hydroxyurea) —– Anti-metabolite	Mechanism not fully known- believed to increase HbF levels in RBCs, decrease neutrophils, increase water content of RBCs, increase deformability of sickled RBCs and decrease RBC adhesion to endothelium	$	Reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises	Weight based dosing; Reduce dose by 50% if CrCl less than 60ml/min; Some formulations may allow for cutting or crushing
Lyfgenia (lovotibeglogene autotemcel) —– Gene therapy	Patient's own CD34+ cells are genetically edited to add copies of the βA-globin gene, which combines with α-globin to produce hemoglobin A (HbA). This HbA results in red blood cells with higher oxygen-binding affinity, reduces HbS levels and also inhibits polymerization of HbS preventing sickling of RBCs	$$$$	Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events	One time treatment; Requires myeloablative conditioning prior to infusion of modified cells; Only administered at Qualified Treatment Centers (QTCs); Total treatment time takes several months
Oxbryta (voxelotor) —– Hemoglobin S poly-merization inhibitor	Binds HbS to prevent polymerization and increase oxygen-binding affinity. Also may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity	$$$	Treatment of sickle cell disease in adults and pediatric patients 4 years of age and older	Available in tablets and tablets for oral suspension; Avoid with strong or moderate CYP3A4 inducers; Dose reduce for severe hepatic impairment (Child Pugh C).; Dosing by body weight for ages 4-12
Zynteglo (betibeglogene autotemcel) —– Gene therapy	Patient's own CD34+ cells are genetically edited to add copies of the βA-globin gene, which combines with α-globin to produce hemoglobin A (HbA). This corrects the β/α-globin imbalance in erythroid cells and has the potential to increase functional adult HbA and total Hb to normal levels	$$$$	Treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions	One time treatment; Requires myeloablative conditioning prior to infusion of modified cells; Only administered at Qualified Treatment Centers (QTCs); Total treatment time takes several months

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  24 hours a day, 7 days a week
- **Maryland Medicaid Pharmacy Access Hotline**
  833-325-0105
  Monday-Friday, 8:00 am - 5:00 pm
- **Kidney Disease Program**
  410-767-5000 or 5002
  Monday-Friday, 8:00 am - 5:00 pm
- **Breast and Cervical Cancer Diagnosis and Treatment**
  410-767-6787
  Monday-Friday, 8:00 am - 4:30 pm
- **Maryland AIDS Drug Assistance Program**
  410-767-6535
  Monday-Friday, 8:30 am - 4:30 pm
- **Peer Review Program**
  855-283-0876
  Monday-Friday, 8:00 am - 6:00 pm

Hemoglobin-impacting Genetic Disorders References:

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- Oxbryta (voxelotor) (accessed 2024 Jan 23)
- Endari (L-glutamine oral powder) (accessed 2024 Jan 23)
- Adakveo (crizanlizumab-tmca) (accessed 2024 Jan 23)
- Droxia (hydroxyurea) (accessed 2024 Jan 23)
- Zynteglo (betibeglogene autotemcel) (accessed 2024 Mar 21)

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