

Use of Hydroxyurea in Adult Patients Diagnosed with Sickle Cell Disease

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Introduction

Sickle cell disease (SCD) is a benign hematologic disorder caused by a point mutation on the beta globin chain which replaces glutamic acid with valine.¹ This disease, occurring mostly in those of African descent, decreases one's lifespan by 20-30 years due to numerous complications.^{2,3} Acute complications may include vaso-occlusive crisis or pain crisis, acute chest syndrome, stroke, priapism, acute renal failure, infection, cholecystitis, and splenic sequestration. Also, SCD negatively impacts the patient's quality of life (QOL).⁴ The main treatment used to prevent and decrease the rate of acute complications is hydroxyurea (HU). HU is thought to prevent sickling of red blood cells by increasing the amount of fetal hemoglobin (HbF), which does not contain beta globin chains.^{5,6}

NIH Guideline Summarization⁴

Indications for HU in patients with SCD

- ≥ 3 moderate to severe pain crises per year or pain that interferes with quality of life (QOL)
- History of recurrent and/or severe ACS
- Symptomatic and severe chronic anemia which interferes with QOL
- Concurrent treatment with erythropoietin agents for chronic kidney disease

HU Dose:

- Starting: 15 mg/kg/day
 - Chronic kidney disease: 5-10 mg/kg/day
- May increase dose by 5 mg/kg/day every 8 weeks based on clinical outcomes and laboratory values
 - Clinical response may take 3-6 months
- Maximum: 35 mg/kg/day
 - Maintain the maximum tolerated dose for a minimum of 6 months prior to discontinuation due to treatment failure
- Round to nearest 500 mg capsule dose; do not open capsules.^{4,7}



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Monitoring:

Laboratory Tests	Before starting HU	Monthly until stable dose	Every 2-3 months with stable dose	When Clinically Relevant
Complete blood count with differential	X	X	X	
Reticulocyte count	X	X	X	
Mean Corpuscular Volume (MCV)	X			X
HbF	X			X
Comprehensive metabolic panel	X			
Liver function	X			
Pregnancy test	X			

Dose adjustments based on toxicity:

- Absolute neutrophil count < 2000/microL and/or platelets < 80,000/microL
 - Hold HU and monitor above laboratory values weekly
 - Once recovered, decrease dose by 5 mg/kg/day

Pregnancy/Breastfeeding:

- Discontinue HU⁴
- Data:
 - None in pregnant women
 - Teratogenic and embryotoxic in animals⁷

Other counseling points:

- Contraception counseling needed in patients of reproductive age⁴
 - Needed during and for 6 months after finishing treatment in women and 1 year in men⁸
- Adherence reinforcement⁴
- Avoid live vaccines⁷

Clinical Evidence

The Multicenter Study of Hydroxyurea in Patients with Sickle Cell Anemia (MSH) has been one of the most influential trials in the treatment of patients with sickle cell disease.⁸ Many of the guideline recommendations are based on this study.

- Population:
 - n=299 adults (≥ 18 years old) with sickle cell anemia including sickle cell-alpha-thalassemia
 - ≥ 3 pain crises in the prior year
 - Exclusions: sickle cell-beta⁺ and beta^o-thalassemia, pregnancy, narcotic addiction, use of > 30 capsules of oxycodone every 2 weeks on a regular basis, enrollment in a long-term transfusion program or received transfusions at time of enrollment with > 15% of hemoglobin A, blood counts similar to that of bone marrow suppression, stroke within 6 years, human immunodeficiency virus antibodies in serum, and prior HU treatment or current treatment with anti-sickling medication

- Study arms:
 - Treatment: HU 15 mg/kg/day increased by 5 mg/kg/day every 12 weeks until maximum of 35 mg/kg/day
 - If bone marrow suppression occurred, dose held and then decreased by 2.5 mg/kg/day once counts normalized
 - Control: placebo
- Efficacy outcomes (HU versus placebo):
 - Median pain crises per year: 2.5 vs. 4.5
 - Pain crises defined as > 4 hour visit at a healthcare facility for sickle cell pain and received intravenous opioids for treatment of pain
 - Hospitalizations due to pain crises per year: 1 vs. 2.4
 - Median months to vaso-occlusive crisis: 3 vs. 1.5
 - Acute chest syndrome (ACS) incidence: 16.4% vs. 34.7%
 - Patients who received transfusions: 31.6% vs. 49.7%
 - No decrease in death, stroke, or hepatic sequestration with HU compared to placebo
 - At a 17.5 years follow-up, death rates were 39.5% vs. 46.9%, with an increased benefit with prolonged use of HU
- Toxicity outcomes:
 - 51% could tolerate the maximum dose by the end of the study
 - Myelosuppression occurred in almost all patients causing holding of HU
 - Recovery of blood counts occurred at 2 weeks in most
 - Treatment discontinued in 9.2% (HU) and 4.1% (placebo)
 - Other side effects: hyperbilirubinemia and parvovirus B19 infection leading to aplastic anemia
 - 10 pregnancies occurred with no noticeable defects at birth
 - No deaths or malignancies were reported related to HU⁸

Conclusion

In adult patients with SCD, HU has been shown to decrease the incidence of pain crises and ACS. The most common adverse effect is myelosuppression, which can be improved by holding HU therapy and restarting at a lower dose. This medication is contraindicated in pregnancy and appropriate contraception counseling is imperative for patients receiving HU. Lastly, adherence to HU is necessary for optimal efficacy outcomes.

References

1. Ingram VM. A specific chemical difference between the globins of normal human and sickle-cell anaemia haemoglobin. *Nature*. 1956;178:792-4.
2. Farrell K, Dent L, Nguyen ML, Buchowski M, Bhatt A, Aguinaga Mdel P. The relationship of oxygen transport and cardiac index for the prevention of sickle cell crises. *J Natl Med Assoc*. 2010;102:1000-7.
3. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330:1639-44.
4. U.S. Department of Health and Human Services. Evidence-based management of sickle cell disease. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed September 9, 2018.
5. Charache S. Fetal hemoglobin, sickling, and sickle cell disease. *Adv Pediatr*. 1990;37:1-31.
6. Charache S, Dover GJ, Moore RD, et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. *Blood*. 1992;79:2555-65.
7. Hydrea [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2016.
8. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *New Engl J Med*. 1995;332:1317-22.

Attention Behavioral Health Services Providers

Louisiana Medicaid has implemented changes required by Senate Bill No. 564 for behavioral health services providers (BHSPs) of Community Psychiatric Support and Treatment (CPST) or Psychosocial Rehabilitation (PSR) Services. Changes include CPST and PSR requirements related to:

- Member Choice Forms;
- Staff educational requirements;
- Staffing;
- Supervision;
- Accreditation;
- Credentialing; and
- Claims payment.

BHSPs must meet all qualifications and requirements in statute, rule and the Medicaid Behavioral Health Services Provider Manual prior to rendering services.

Providers can review [Informational Bulletin 18-14](#) for additional details. Updates to the provider manual inclusive of effective dates are forthcoming and will be found at www.lamedicaid.com under the Provider Manuals link within the Behavioral Health Services Manual.

Questions related to managed care should be directed to the appropriate Managed Care Organization (MCO).

PHARMACY FACTS

Program Updates from Louisiana Medicaid

Pharmacy Facts can also be found online at: <http://ldh.la.gov/index.cfm/page/3036>.

February 15, 2019

UnitedHealthcare brand drug reimbursement

On February 10, 2019, UnitedHealthcare (BIN 610494, PCN 9999, Group ACULA), one of the five managed care organizations (MCOs) contracted with Medicaid for service delivery, updated an average acquisition cost (AAC) file. This resulted in some issues with the reimbursement on ingredient cost on some brand name drugs. The file was corrected on February 12, 2019.

UnitedHealthcare will be reaching out by telephone to impacted pharmacies so that claims can be reprocessed for updated reimbursement. If you have questions please call the UnitedHealthcare Pharmacy Director, Travis Ortiz, at (504) 849-1546.

Generic Tamiflu rate

The Louisiana Department of Health (LDH) was made aware of an AAC rate issue for oseltamivir (generic Tamiflu) suspension. Myers and Stauffer reviewed and updated the rate retrospectively to January 25, 2019. The new rate was sent to the MCOs in this week's file on February 14, 2019. The MCOs have seven days to program new rates, clearing the way for claims to be reprocessed on February 22, 2019 for the updated rate.

Single preferred drug list update

LDH and the MCOs are currently coding drug files and working with programmers to implement the single preferred drug list (PDL) on May 1, 2019. The single PDL is the product of a collaborative administrative simplification effort for both prescribers and pharmacists who provide care to Medicaid members.

The single PDL will align all preferred drugs across fee-for-service Medicaid and the five MCOs. The list of drugs that require prior authorization will also be consistent. In preparation of the transition to a single PDL, notifications will be sent on March 1 to recipients and providers if the single PDL will cause a current preferred medication to require a prior authorization after May 1.

February 1, 2019

Medicaid single preferred drug list implementation planned for May

The transition to a single preferred drug list (PDL) for all managed care organizations (MCOs) and Medicaid fee-for-service remains on schedule for a May 1, 2019 implementation date.

Medicaid is actively working toward the May go-live date, including the necessary state rulemaking and amendments to our state plan with CMS. The changes to the pharmacy program will also include a change in the dispensing fee and a change in the ingredient cost methodology from the average acquisition cost (AAC) to the national average drug acquisition cost (NADAC). Although the dispensing fee and NADAC changes are only applicable to fee-for-service Medicaid, MCOs are mandated (through legislation) to reimburse local pharmacies at the fee-for-service rate. Additional background on the single PDL can be found in previous editions of Pharmacy Facts.

Pharmacy co-payment changes scheduled for 2019, 2020

Beginning April 1, 2019, Medicaid will implement a temporary co-payment structure to comply with a CMS requirement that limits cost-sharing to no more than 5 percent of family income each month.

Currently, Louisiana Medicaid imposes no limit on the amount of pharmacy copays a recipient may pay. To comply with the federal 5-percent limit, Medicaid will use a new income-based copay tier from April 1 through December 31, 2019. This will establish a \$0 copay for all pharmacy claims for families with income less than or equal to \$800 a month. This income tier was developed using state fiscal year (SFY) 2018 data and is designed to eliminate all cost-sharing overpayments for this population in the short term.

Medicaid has begun systemic programming to provide a long-term solution to copay overpayments. The changes will automatically prevent copayments being charged over the 5-percent family threshold. This method will replace the income-based copay tier beginning January 1, 2020.

No action is required of pharmacy providers to effect these copay changes.

Pharmacy reimbursement and Louisiana Register notifications

In the January 2019 edition of the Louisiana Register, Medicaid published a Notice of Intent (NOI) for the pharmacy program's reimbursement changes from average acquisition cost (AAC) to the national average drug acquisition cost (NADAC). Because NADAC is equal to a drug's Federal Upper Limit (FUL), Medicaid originally intended to eliminate consideration of the FUL in the reimbursement methodology. This was included in the January notice.

Following more recent guidance from CMS, Medicaid will continue the use of FUL in its NADAC reimbursement method, as with AAC. This edit will be noted in a submission of a second NOI, to be published in the February 2019 edition of the Louisiana Register. The combination of both rule changes will allow the implementation of the reimbursement change to NADAC, which will be implemented on May 1, 2019.



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Eligibility and Enrollment System Provider Bulletins

Louisiana Medicaid is publishing bi-weekly provider bulletins to address provider questions and concerns around the new eligibility and enrollment system. The information in these bulletins covers a wide range of provider issues and provider types. This and other news can be found on the web site dedicated to the new system, found here:

<http://ldh.la.gov/index.cfm/page/3497>.

If there are topics you feel need to be covered in these public communications, please let us know by sending an email to Healthy@la.gov.

Online Medicaid Provider Manual Chapter Revisions as of February 2019

Manual Chapter	Section(s)	Date of Revision(s)
Dental Services	16.5 Early And Periodic Screening, Diagnosis And Treatment (EPSDT) - Covered Services	02/12/19
Dental Services	16.5 Early And Periodic Screening, Diagnosis And Treatment (EPSDT) - Covered Services	02/27/19
Professional Services	Table of Contents 5.1 Covered Services – Laboratory and Radiology Services Non-Invasive Prenatal Testing	02/01/19

Archived Online Medicaid Provider Manual Chapter Revisions as of February 2019

Manual Chapter	Section(s)	Date of Omission(s)
Dental Services	16.5 Early And Periodic Screening, Diagnosis And Treatment (EPSDT) - Covered Services –	02/06/19
Dental Services	16.5 Early And Periodic Screening, Diagnosis And Treatment (EPSDT) - Covered Services –	02/12/19
Professional Services	Table of Contents 5.1 Covered Services – Laboratory and Radiology Services Non-Invasive Prenatal Testing	03/13/18

Remittance Advice Corner

2019 Allowed Procedures for Assistant Surgeon and Assistant at Surgery Providers

Louisiana Medicaid has published the 2019 fee for service list of allowed procedures for assistant surgeon and assistant at surgery providers. The list titled, “2019 Assistant Surgeon and Assistant at Surgery List of Covered Procedures” has been posted to the LA Medicaid website (www.lamedicaid.com) under the ClaimCheck icon.

The changes are based on updates made by the Change Healthcare to their ‘ClaimCheck’ product. Change Healthcare uses the American College of Surgeons as its primary source for determining assistant surgery designations.

This list does not ensure payment but provides a comprehensive list of codes that may be allowed when billed by an assistant surgeon or by an assistant at surgery.

For questions related to this information as it pertains to fee-for-service Medicaid claims processing, please contact DXC Technology Provider Services at (800) 473-2783 or (225) 924-5040.

Please contact the appropriate Managed Care Organization with any questions concerning their 2019 HCPCS updates.

2019 HCPCS and Physician-Administered Drug Reimbursement Updates

The Louisiana Medicaid fee-for-service (FFS) files have been updated to reflect the new and deleted Healthcare Common Procedure Coding System (HCPCS) codes effective for dates of service on or after January 1, 2019. Providers will begin to see these changes on the remittance advice of February 5, 2019. Claims that have been denied due to use of the new 2019 codes prior to their addition to the claims processing system will be systematically recycled with no action required by providers.

Effective for dates of service beginning on January 1, 2019, Louisiana Medicaid updated the reimbursement rates on the FFS file for physician-administered drugs and payable vaccines in the physician office setting to align with the Medicare 2019 Average Sale Price (ASP) drug rate or wholesale acquisition cost. Claims previously submitted for these drugs or vaccines with dates of service on or after January 1, 2019 will be systematically adjusted to ensure proper payment. No action is required by the provider.

For questions related to this information as it pertains to fee-for-service Medicaid claims processing, please contact DXC Technology Provider Services at (800) 473-2783 or (225) 924-5040.

Please contact the appropriate Managed Care Organization with any questions concerning their 2019 HCPCS updates.



For Information or Assistance, Call Us!

Provider Enrollment	(225)216-6370	General Medicaid Eligibility Hotline	1-888-342-6207
Prior Authorization: Home Health/EPSTD – PCS	1-800-807-1320	MMIS Claims Processing	(225) 342-3855
Dental	1-866-263-6534 1-504-941-8206	Resolution Unit	
DME & All Other	1-800-488-6334 (225) 928-5263	MMIS/Recipient Retroactive Reimbursement	(225) 342-1739 1-866-640-3905
Hospital Pre-Certification	1-800-877-0666	Medicare Savings Program and Medicaid Purchase Hotline	1-888-544-7996
REVS Line	1-800-776-6323 (225) 216-(REVS)7387		
Point of Sale Help Desk	1-800-648-0790 (225) 216-6381	For Hearing Impaired	1-877-544-9544
		Pharmacy Hotline	1-800-437-9101
		Medicaid Fraud Hotline	1-800-488-2917