L-Glutamine (Endari™) Abbreviated New Drug Update (ANDU)

March 2019

OVERVIEW[1,2]

- Indications
  - L-glutamine oral powder (Endari) is an amino acid indicated to reduce the acute complications of sickle cell disease (SCD) in adults and children 5 years and older.
- Contraindications/Warnings
  - They are no contraindications or boxed warnings for L-glutamine oral powder (Endari).
- Adverse Reactions
  - The most common adverse reactions reported in clinical trials in > 10% of patients were constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain.
- Drug Interactions
  - No drug interaction studies were conducted.
- Special Populations
  - Pregnancy- There is no available data on L-glutamine use in pregnant or lactating women to inform a drug-associated risks of major birth defects or miscarriage.
  - Pediatrics- L-glutamine is indicated for use in adults and pediatric patients ≥ 5 years of age; the safety and efficacy in patients < 5 years of age have not been established.
- Availability
  - Oral powder containing 5 grams of L-glutamine powder per paper-foil-plastic laminate packet (carton of 60 packets).
- Dosage
  - Administered twice daily as a 5 to 15 gram dose orally, based on body weight. The dose is mixed in 8 oz. of cold or room temperature beverage or 4 oz. to 6 oz. of food before administration.
- Clinical Trials[3,4,5]
  - Efficacy was established in a randomized, double-blind, placebo-controlled, parallel group study with a treatment duration of 48-weeks followed by 3 weeks of tapering.
  - The study included patients ≥ 5 years of age (n=230) who had 2 or more painful crises within 12 months of the screening visit. Patients were randomized in a 2:1 ratio of 0.3 g/kg of L-

glutamine (n=152) or placebo (n=78). Patients receiving concurrent hydroxyurea or receiving blood transfusions were permitted into study. Enrollment exclusions included significant medical conditions that required hospitalization within 2 months of screening, prothrombin INR > 2, serum albumin < 3 g/dL, patients receiving blood products within 3 months of screening, pregnant or lactating females, a history of uncontrolled liver disease or renal insufficiency, and those currently taking or previously treated with an investigational medication within 30 days of screening.

- The primary efficacy endpoint was the number of sickle cell crises (SCC) defined as emergency room or medical facility visits related to SCC pain that was then treated with a parenterally administered narcotic or ketorolac. SCC was also defined as the occurrence of acute chest syndrome (ACS), priapism, and splenic sequestration.
  - The study demonstrated significantly lower SCC in the L-glutamine treatment group versus placebo over the 48 weeks (p=0.005) with the L-glutamine group having 1 less sickle cell crisis (mean of 3 versus 4 with placebo).
  - An improvement was seen in median days to first sickle cell crisis (84 for the L-glutamine group versus 54 for placebo) and median cumulative days in hospital (6.5 for the L-glutamine group versus 11 for placebo).

CLINICAL CONSIDERATIONS[6,7,8,9,10,11]

- Sickle cell disease (SCD) affects about 100,000 patients in the United States (US) and primarily affects African Americans, Latinos, and other minorities. It results in a host of acute and chronic complications, including vasoocclusion and hemolysis. Patients with this genetic disorder have an average life expectancy of 40 to 60 years.
- In SCD, the exact mechanism of action of L-glutamine is unknown. It may increase the availability of reduced glutathione, which plays a role in protecting cells from oxidative stress.
- Endari is the second FDA approved treatment for SCD in adults, with the first being hydroxyurea, which was approved for use in adults in 1998. Hydroxyurea capsules prevent vasoocclusive events in SCD. Endari was the first treatment approved for use in children with SCD. Later in 2017, a new formulation of hydroxyurea, Siklos®, was approved for use in SCD children ≥ 2 years old with recurrent moderate to severe painful crises to reduce the frequency of painful crises and blood transfusions.
- Hydroxyurea is considered a mainstay of management of SCD; however, Endari offers an option for those with suboptimal response as adjunctive therapy or for use in those intolerable to hydroxyurea. Blood transfusions also can be used to treat and prevent complications of SCD, but the only curative option for SCD is hematopoietic cell transplantation. Guidelines for the management of SCD from the National Heart, Lung, and Blood Institute, which support the use of hydroxyurea to decrease crises in SCD patients, were published prior to the availability of Endari and Siklos. The American Society of Hematology (ASH) is developing new guidelines on the management of SCD; the publication is anticipated in 2019.

- The active component of Endari, L-glutamine, is also available as an over-the-counter nutritional supplement.
- Emmaus Medical's Endari is currently available.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	N/A
Clinical Edit	**Initial Approval Criteria** ▪ Coverage is provided in the following conditions: – Patient is ≥ 5 years old; **AND** – Patient has a diagnosis of sickle cell anemia; **AND** – Dosage is appropriate based on body weight. **Renewal Criteria** ▪ Patient must continue to meet initial criteria.
Quantity Limit	30 grams per day (maximum of 6 packets/day)
Duration of Approval	Initial: 1 year Renewal: 1 year
Drug to Disease Hard Edit	None

REFERENCES

1 Endari [package insert]. Torrance, CA; Emmaus Medical; August 2017.
2 Oncology Drug Advisory Committee. Oral L-glutamine powder for the treatment of sickle cell disease. Emmaus Medical Inc., May 24, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559736.pdf Accessed March 7, 2019.
3 Endari [package insert]. Torrance, CA; Emmaus Medical; August 2017.
2 Oncology Drug Advisory Committee. Oral L-glutamine powder for the treatment of sickle cell disease. Emmaus Medical Inc., May 24, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559736.pdf Accessed March 7, 2019.
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Hydroxyurea (Siklos®) Abbreviated New Drug Update (ANDU)

March 2019

OVERVIEW[1]

- Hydroxyurea (Siklos), an antimetabolite, is indicated for the reduction in frequency of painful crises and to reduce the need for blood transfusions in pediatric patients ≥ 2 years old with sickle cell anemia with recurrent moderate to severe painful crises.
- Contraindications- known hypersensitivity
- Warnings
  - Boxed warnings
    - Severe myelosuppression- do not give hydroxyurea if bone marrow function is markedly depressed; blood counts should be monitored before and throughout therapy; dose may need to be interrupted or reduced as necessary
    - Carcinogenic- patients should wear sun protection and monitor for malignancies
  - Other warnings- embryofetal toxicity; cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene; pancreatitis, hepatotoxicity, and peripheral neuropathy with concurrent antiretroviral drugs; risks with concomitant use of live vaccines; macrocytosis, generally self-limiting and early in treatment (prophylactic folic acid use recommended); and falsely elevated uric acid, urea, or lactic acid assay results
- Drug Interactions
  - Pancreatitis, peripheral neuropathy, hepatotoxicity, and/or hepatic failure, some fatal, with didanosine (± stavudine); do not use concomitantly.
  - Avoid live virus vaccines; may potentiate the replication of the vaccine virus and/or increase the adverse reactions of the vaccine
- Common Adverse Effects
  - The most common (> 10%) adverse effects include infections (39.8%) and neutropenia (12.6%).
- Special Populations
  - Pregnancy
    - Can cause fetal harm, but available data of it use in pregnancy are insufficient to inform drug-associated risks
    - Establish pregnancy status prior to starting therapy. Women and men should use effective contraception during therapy and for 6 months after stopping treatment.

- Pediatrics
    - Efficacy and safety of hydroxyurea have been established in patients 2 to 18 years old. Patients aged 2 through 16 years have a higher risk of neutropenia compared to older pediatric patients.
    - Growth monitoring recommended
- Renal impairment
    - Dose adjustment recommended for estimated creatinine clearance (CrCl) < 60 mL/min and end-stage renal disease (ESRD).

- Availability
    - Tablets- 100 mg and functionally triple-scored 1,000 mg. The 1,000 mg tablets have 3 score lines and can be split into 4 parts (250 mg each); do not split into smaller parts.
- Dosage
    - Initial dose- 20 mg/kg once daily based on actual or ideal body weight, whichever is less
        - Administer once daily with water. Tablets can be dispersed in a small amount of water in a teaspoon for immediate use for those unable to swallow tablets.
    - Dose adjustments
        - Patient's blood should be monitored every 2 weeks. The dose may be increased by 5 mg/kg/day every 8 weeks, or sooner, if a severe painful crisis occurs, until a maximum tolerated dose or 35 mg/kg/day is obtained, if blood tests are in an acceptable range.
        - If blood counts are considered toxic, hydroxyurea should be discontinued until hematologic recovery. Therapy can be resumed at a 5 mg/kg/day reduction from the dose that caused the hematological toxicity.
        - Reduce dose by 50% in patients with a CrCl < 60 mL/min or ESRD.
    - Hydroxyurea is a cytotoxic drug; patients should follow applicable special handling and disposal procedures. See prescribing information for additional details.
- Clinical Trials
    - The European Sickle Cell Disease Cohort study (ESCORT HU), an open-label, single-arm study, assessed the safety and effectiveness of hydroxyurea tablets in 405 pediatric patients ages 2 to 18 years old with sickle cell disease (SCD). Treatment was assessed for ≥ 12 months (median, 23 months; range, 12 to 80) in evaluable patients. Notably, 141 of the included patients had not been previously treated with hydroxyurea. The median fetal hemoglobin (HbF) percentages were 5.6% (range, 1.3 to 15) and 12.8% (range, 2.1 to 37.2) at baseline and ≥ 6 months after starting hydroxyurea therapy, respectively, with median change of 5.9% (range, -2.2 to 34.7) in 47 patients. The median hemoglobin levels were 8.2 g/dL (range, 3.7 to 14.2), 8.8 g/dL (range, 0.7 to 13.1), and 8.9 g/dL (range, 5.5 to 13.2) at baseline, approximately 6 months, and approximately 12 months, respectively, after starting hydroxyurea therapy. The median change was 0.5 g/dL (range, -4.6 to 6.1) in 63 patients and 0.7 g/dL (range, -6.4 to 6) in 83 patients at approximately 6 months and 12 months, respectively, after starting hydroxyurea

therapy. The number of patients with ≥ 1 vaso-occlusive episode (69.2% versus 42.5%, respectively), ≥ 1 acute chest syndrome episode (23.6% versus 5.7%, respectively), ≥ 1 hospitalization related to SCD (75.5% versus 41.8%, respectively), and ≥ 1 blood transfusion (45.9% versus 23%, respectively) 12 months before and 12 months after hydroxyurea therapy were compared in the patient population not been previously treated with hydroxyurea.

CLINICAL CONSIDERATIONS[2,3,4,5]

- Sickle cell disease (SCD) affects about 100,000 patients in the United States (US) and primarily affects African Americans, Latinos, and other minorities. It results in a host of acute and chronic complications, including vaso-occlusion and hemolysis. Patients with this genetic disorder have an average life expectancy of 40 to 60 years.
- In SCD, the exact mechanism of action of hydroxyurea is unknown. It may inhibit DNA synthesis by acting as a ribonucleotide reductase inhibitor.
- Hydroxyurea capsules were approved for use in 1998 to prevent vaso-occlusive events in adults with SCD. L-glutamine (Endari™), approved in 2017 was the first treatment approved for use in children with SCD; however, it is generally for use in those unable to tolerate hydroxyurea or as adjunctive therapy for those with suboptimal response on hydroxyurea. Siklos was approved in December 2017.
- Hydroxyurea is considered a mainstay of management of SCD. Guidelines for the management of SCD from the National Heart, Lung, and Blood Institute support the use of hydroxyurea to decrease crises in SCD patients. Recommendations in these guidelines include the following:
  - Hydroxyurea can reduce the occurrence of sickle cell-related pain and the incidence of acute chest syndrome (ACS).
  - Hydroxyurea should be used adults with sickle cell anemia who have ≥ 3 sickle cell-associated moderate to severe pain crisis within a 12 month period (Strong Recommendation, High-Quality Evidence). Adults with sickle cell anemia pain that interferes with daily activities/ quality of life; have a history of severe and/or recurrent ACS; or who have severe symptomatic chronic anemia that interferes with daily activities/quality of life should also be treated with hydroxyurea (Strong Recommendation, Moderate-Quality Evidence).
  - In children ≥ 9 months with sickle cell anemia, hydroxyurea treatment should be offered without regard to clinical severity to reduced sickle cell disease related complications (Strong Recommendation, High-Quality Evidence for ages 9 to 42 months; Moderate Recommendation, Moderate-Quality Evidence for children > 42 months and adolescents).
  - Females who are pregnant or breastfeeding should discontinue hydroxyurea therapy (Moderate Recommendation, Very Low-Quality Evidence).
  - Guidelines were published prior to the availability of Endari and Siklos.
- The American Society of Hematology (ASH) is developing new guidelines on the management of SCD; the publication is anticipated in 2019.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	N/A
Clinical Edit	**Initial Approval Criteria** Coverage is provided in the following conditions: • Patient is ≥ 2 years old; **AND** • Patient has a diagnosis of sickle cell anemia with recurrent moderate to severe painful crisis; **AND** • Patient does not have a history of hypersensitivity to hydroxyurea or any other component of its formulation; **AND** • Patient's baseline blood counts have been performed; **AND** • If patient is of childbearing potential, it is documented that the patient is not pregnant or breastfeeding and has been educated on the need for effective contraception during and for 6 months after therapy. **Renewal Criteria** Patient must: • Continue to meet initial criteria; **AND** • Have evidence of blood counts every 2 weeks within normal range: – Neutrophils ≥ 2,000 cells/mm^{3*}; **AND** – Platelets ≥ 80,000/mm^3; **AND** – Hemoglobin ≥ 5.3 g/dL; **AND** – Reticulocytes ≥ 80,000/mm^3 if the hemoglobin concentration is < 9 g/dL; **AND** – Not have had > 1 hematologic toxicity * Younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/mm^3
Quantity Limit	20 to 35 mg/kg/day based on ideal or actual body weight, whichever is less, noting the 1,000 mg tablet can be functionally split into 4 parts (250 mg increments) when calculating quantity needed for the month
Duration of Approval	Initial: 6 months Renewal: 1 year
Drug to Disease Hard Edit	Pregnancy; lactation

REFERENCES

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