CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	14 Dec 2017
From	Nicole Gormley, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208843
Applicant	Addmedica SAS
Date of Submission	30 Jun 2017 (Class-2 Resubmission)
PDUFA Goal Date	30 Dec 2017
Proprietary Name / Established (USAN) names	Siklos ®/ hydroxyurea
Dosage forms / Strength	Tablet: 100 mg, 1,000 mg Quadri-scored
Proposed Indication	1. To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises
Recommended Action:	Approval

Material Reviewed/Consulted	**Reviewer**
Clinical Review	Rachel Ershler, MD
Nonclinical Pharmacology/toxicology	Matthew Thompson, PhD, MPH; Christopher Sheth, PhD
Clinical Pharmacology Review	Guoxiang Shen, Ph.D.; Bahru Habtemariam, PharmD.
Product Quality Review	Rohit Tiwari, PhD; Xing Wang, PhD; Mei Ou, PhD; Okpo Eradiri, PhD; Angelica Dorantes, PhD; Anamitro Banerjee, PhD
Patient Labeling Review; Division of Medical Policy Programs	Barbara Fuller, RN, MSN, CWOCN; Morgan Walker, PharmD, MBA, CPH; Ruth Lidoshore, PharmD; Rachel Conklin, MS, RN
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Rhiannon Leutner, PharmD, MPH, MBA; Hina Mehta, PharmD

1. Introduction

On July 29, 2016, Addmedica SAS (Applicant) submitted a 505(b)(2) application (NDA 208843) for Siklos ®, hydroxyurea. Droxia® (Bristol Myers Squibb, NDA 016295) was the reference listed drug for this 505(b)(2) application. The application received a complete response on February 9, 2017. (b) (4) [redacted].

On June 30, 2017, the Applicant resubmitted their NDA.

The proposed indication is "to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises."

The dosing regimen proposed for this indication is:

- Initial dose: 20 mg/kg/day as a single dose (b) (4). The patient's blood count must be monitored every two weeks.
- The dose may be increased- if blood counts are in the acceptable range- by 5 mg/kg/day every 8 weeks or sooner if a severe painful crisis occurs, until mild myelosuppression up to a maximum of 35 mg/kg/day is reached.

This 505(b)(2) application is primarily supported by the results from the ESCORT-HU Study, a multicenter, prospective, non-interventional cohort study sponsored by Addmedica. The application also relies upon relevant non-clinical and clinical published data and the FDA's previous findings of safety and effectiveness of Droxia®.

In response to the CR, the Applicant submitted (b) (4) additional dissolution data. The Division of Biopharmaceutics reviewed the submitted data and now recommends approval of the NDA.

2. Background

Sickle Cell Disease (SCD) is an inherited disorder that results from a point mutation in the beta (β)-globin chain, resulting in the production of Hemoglobin (Hb) S. Several SCD genotypes exist, including homozygous Hb S (HbSS) and the compound heterozygous conditions including Hemoglobin $S\beta^0$-thalassemia ($HbS\beta^0$-thal), hemoglobin $S\beta^+$-thalassemia, and hemoglobin SC(1). The most prevalent genotype HbSS and the less common $HbS\beta^0$- thal are commonly referred to as sickle cell anemia, as they are clinically similar and associated with the most severe clinical manifestations.

The major clinical manifestations of SCD are related to hemolytic anemia and vaso-occlusion. SCD can result in a variety of clinical manifestations and complications including: acute vaso-occlussive crises (VOCs), chronic pain, chronic hemolytic anemia, recurrent infections, and neurologic complications. Additionally, vascular injury from chronic ischemia leads to multi-organ dysfunction and early mortality.

Siklos®, hydroxyurea, is an antimetabolite and an antineoplastic drug. In patients with sickle cell disease, the pharmacologic effects of hydroxyurea that may contribute to its beneficial effects include increasing hemoglobin F levels in red blood cells, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium(2).

Although there is not an approved indication for the use of hydroxyurea (including Droxia®) in pediatric patients with SCD, there has been a long-standing use of hydroxyurea in pediatric

patients and its use is recommended in practice guidelines(3). Siklos® was approved in the EU in June 2007 for the treatment of sickle cell disease in both adult and pediatric patients. The EMA required a Risk Management Plan to collect information regarding the safety of Siklos®. ESCORT-HU was conducted to meet the requirements of the Risk Management Plan. In pre-NDA meetings held with the FDA in December 2014 and October 2014, it was agreed that the Applicant would compile clinical efficacy and safety data from ESCORT-HU in pediatric patients to support a 505(b)(2) marketing application in the US.

3. CMC/Device

Source: Excerpted from the Quality Assessment Review from the Office of Product Quality. Please see their review for additional details.

The Division of Biopharmaceutics had reviewed the overall information provided under NDA 208843 (Original and Resubmission) and has the following comments:

1. The dissolution method and acceptance criterion as described below are acceptable for batch release and stability testing of Siklos® (hydroxyurea) Tablets, 100 mg and 1000 mg.

FDA's Approved Dissolution Test for Siklos® (hydroxyurea) Tablets, 100 and 1000 mg	
Dissolution Method	
USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	Demineralized water
Dissolution Volume	500 mL (Siklos 100 mg tablets); 1000 mL (Siklos 1000 mg tablets and ¼ split portions of Siklos 1000 mg tablets)
Temperature	37°C ± 0.5°C
Sampling Time Points	5, 10, 15, and 30 minutes
Dissolution Acceptance Criterion	Q= (b)(4)% in 15 minutes

2. As per 21 CFR 320.21(b)(5/6), the overall *in vitro* and *in vivo* information/data provided by the Applicant is deemed adequate and acceptable to establish the scientific bridge between the listed drug product, Droxia® (hydroxyurea) Capsules and the proposed Hydroxyurea Tablets.

Based on the above, the Division of Biopharmaceutics recommends approval of NDA 208843 for Siklos® (hydroxyurea) 100 and 1,000 mg tablets.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology/toxicology review by Drs. Thompson and Sheth.

The Applicant is relying on published nonclinical data and the FDA's previous findings of safety and effectiveness for Droxia®. The Applicant has not submitted any new nonclinical studies in support of the NDA approval for hydroxyurea, 100 and 1,000 mg tablets. The nonclinical section (Module 4) only has literature references. The NDA submission emphasizes findings from an expert panel report published in 2007 by Liebelt, et al. titled "NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea". This report, and other literature in the submission, adequately addresses Pharmacology/Toxicology concerns from the pre- NDA meeting on December 11, 2014.

Pharmacology/Toxicology was consulted by CMC regarding a newly identified degradation product. Based on qualification by use, Pharmacology/Toxicology has no concerns with the degradation product (b) (4).

Pharmacology/toxicology reviewed the nonclinical sections of the label and participated in labeling negotiations with the Applicant.

The Division of Hematology and Oncology Toxicology determined that hydroxyurea (Siklos®) could be approved for the proposed indication.

5. Clinical Pharmacology

Source: Pharmacology/toxicology review by Drs. Shen and Habtemariam.

The clinical pharmacology review states that the NDA is approvable from a clinical pharmacology perspective. No new clinical pharmacology information was included in the submission for review.

6. Clinical Microbiology

Not applicable.

7. Clinical – Efficacy & Safety

Source: Clinical Review by Dr. Ershler. Please see her review for additional details.

There were no clinical deficiencies identified in the initial review and the clinical team recommended approval at that time.

The resubmission included a safety update. At the time of the data cutoff for this submission (February 17, 2017), the overall number of subjects (adult and pediatric patients) enrolled on ESCORT-HU who received Siklos® increased from 992 to 1294. Of these, a total of 627

subjects were ≤18 years of age (increased from 405 in the previous submission). There were no new safety signals identified and the safety profile of Siklos® is unchanged.

The clinical review team recommends approval.

8. Advisory Committee Meeting

This application was not presented to the Oncologic Drug Advisory Committee.

9. Pediatrics

This application sought only a pediatric indication. A Written Request was not issued for this product. All other relevant pediatric discussions are contained within the other review sections.

10. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Financial disclosures:** In accordance with 21 CFR 54, the Applicant submitted financial disclosure information for investigators. There were no investigators from study ESCORT-HU who reported financial interest of arrangements.
- **Other GCP issues:** None
- **OSI audits:** OSI audits were not requested for the clinical sites.

11. Labeling

DMEPA, DMPP, OPDP and the Division's Associate Director for Labeling participated in labeling discussions and provided recommendations.

The Medication Guide (MG) and Instructions for Use (IFU) were revised to be consistent with the Prescribing Information. The PI, MG, and IFU were revised to be consistent with the approved Droxia label, where appropriate. A major ongoing issue at the time initial labeling negotiations were ceased was the instruction to use gloves when handling Siklos®. Ultimately, the IFU was revised to include images of gloved hands during preparation. DMEPA performed a risk assessment of the proposed Siklos PI, MG, IFU, the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

Ultimately, through negotiations with the Applicant, we reached agreement on acceptable labeling.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

  The efficacy and safety results of the ESCORT-HU study demonstrate an acceptable benefit-risk profile for Siklos® for the proposed indication, "to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises". The OPQ, Clinical, Clinical Pharmacology and Pharmacology/toxicology teams all deemed that this application was approvable for the proposed indication. I recommend that this application receive full approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Not applicable

- Recommendation for other Postmarketing Requirements and Commitments

  Not applicable

- Recommended Comments to Applicant

  None

References:

1. MEIER E. R., MILLER J. L. Sickle cell disease in children, Drugs 2012: 72: 895-906.
2. GREEN N. S., BARRAL S. Emerging science of hydroxyurea therapy for pediatric sickle cell disease, Pediatr Res 2014: 75: 196-204.
3. YAWN B. P., BUCHANAN G. R., AFENYI-ANNAN A. N., BALLAS S. K., HASSELL K. L., JAMES A. H. et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members, JAMA 2014: 312: 1033-1048.

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/s/

NICOLE J GORMLEY
12/14/2017

Cross-Discipline Team Leader Review

Date	2 Feb 2017
From	Nicole Gormley, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208843
Applicant	Addmedica SAS
Date of Submission	29 Jul 2016
PDUFA Goal Date	29 Apr 2017 (Major Amendment Issued)
Proprietary Name / Established (USAN) names	Siklos ®/ hydroxyurea
Dosage forms / Strength	Tablet: 100 mg, 1000 mg Quadri-scored
Proposed Indication	1. To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises
Recommended:	Complete Response

Material Reviewed/Consulted	**Reviewer**
Combined Clinical/ Statistical Review	Rachel Ershler, MD
	Yaping Wang, Ph.D.; Yuan-Li Shen, DrPH
Nonclinical Pharmacology/toxicology	Matthew Thompson, PhD, MPH; Christopher Sheth, PhD
Clinical Pharmacology Review	Guoxiang Shen, Ph.D.; Bahru Habtemariam, PharmD.
Product Quality Review	Rohit Tiwari; Xing Wang; Quamrul Majumder; Laura Fontan; Mei Ou; Rabiya Laiq; Anamitro Banerjee
Patient Labeling Review; Division of Medical Policy Programs	Morgan Walker, PharmD, MBA, CPH; Rachel Conklin, MS, RN
Office of Prescription Drug Promotion (OPDP) Consult	Rachel Conklin, MS, RN
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Rhiannon Leutner, PharmD, MPH, MBA; Hina Mehta, PharmD; Lubna Merchant, MS, PharmD.

1. Introduction

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from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises."

The dosing regimen proposed for this indication is:

- Initial dose: 20 mg/kg/day as a single dose before breakfast. The patient's blood count must be monitored every two weeks.
- The dose may be increased- if blood counts are in the acceptable range- by 5 mg/kg/day every 8 weeks or sooner if a severe painful crisis occurs, until mild myelosuppression up to a maximum of 35 mg/kg/day is reached.

This 505(b)(2) application is primarily supported by the results from the ESCORT-HU Study, a multicenter, prospective, non-interventional cohort study sponsored by Addmedica. The application also relies upon relevant non-clinical and clinical published data and the FDA's previous findings of safety and effectiveness of Droxia®.

(b) (4)

2. Background

Sickle Cell Disease (SCD) is an inherited disorder that results from a point mutation in the beta (β)-globin chain, resulting in the production of Hemoglobin (Hb) S. Several SCD genotypes exist, including homozygous Hb S (HbSS) and the compound heterozygous conditions including Hemoglobin $S\beta^0$-thalassemia ($HbS\beta^0$-thal), hemoglobin $S\beta^+$-thalassemia, and hemoglobin SC(1). The most prevalent genotype HbSS and the less common $HbS\beta^0$- thal are commonly referred to as sickle cell anemia, as they are clinically similar and associated with the most severe clinical manifestations.

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increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium(2).

Although there is not an approved indication for the use of hydroxyurea (including Droxia®) in pediatric patients with SCD, there has been a long-standing use of hydroxyurea in pediatric patients and its use is recommended in practice guidelines(3). Siklos® was approved in the EU in June 2007 for the treatment of sickle cell disease in both adult and pediatric patients. The EMA required a Risk Management Plan to collect information regarding the safety of Siklos®. ESCORT-HU was conducted to meet the requirements of the Risk Management Plan. In pre-NDA meetings held with the FDA in December 2014 and October 2014, it was agreed that the Applicant would compile clinical efficacy and safety data from ESCORT-HU in pediatric patients to support a 505(b)(2) marketing application in the US.

3. CMC/Device

Source: Quality Assessment Review from the Office of Product Quality.

The hydroxyurea drug substance is white to almost white crystalline powder that is freely soluble in aqueous but practically insoluble in ethanol. The drug substance is manufactured by (b) (4). The drug substance manufacturing process is briefly described in the submission. A detailed description of the manufacturing process, controls and testing are provided in the DMF. The applicant has referred to the DMF (b) (4) for the description and manufacturing process of the drug substance. The DMF (b) (4) was reviewed by Dr. Rohit Tiwari on January 06, 2017 and was found to be adequate. The spectroscopic data provided in the submission in support of the proposed structure of the drug substance and specified impurities were found to be adequate. The specifications proposed by the applicant are acceptable. Stability data provided by the applicant supports the proposed retest date of (b) (4) under long term storage conditions of (b) (4) RH.

The facility reviewer found the (b) (4) drug substance manufacturing facility acceptable based on previous inspection (b) (4)

The drug product is a film coated tablet available in two strengths, 100 mg and 1000 mg. The 1000 mg tablet has score lines so that it may be divided into four equal parts, allowing flexible dosing in 100 mg and 250 mg intervals. The 100 mg tablet is a white to off-white, round biconvex tablet engraved "100" on one side and with a diameter of approx. 6 mm. The 1000 mg tablet is a white to off-white capsule shaped tablet engraved "┬┴┬┴"on one side, with three breaking notches on both the sides with a length of approximately 22 mm.

The drug product is manufactured, tested, and packaged by (b) (4). No novel excipients or excipients with human or animal origin are used. Apart from the API, which constitutes 71.25% of the tablet weight, the tablets contain silicified microcrystalline cellulose, sodium stearyl fumarate, aminomethacrylate copolymer, (b) (4). All the ingredients are compendial grade. The drug product manufacturing process includes (b) (4)

(b) (4) film coated and packaged in HDPE bottles (60 tablets in 15 mL bottles for 100 mg tablets and 30 tablets in 75 mL bottles for 1000 mg tablets). A detailed description of the manufacturing process, critical steps, and controls are provided in the submission and are found adequate. The drug product release specifications includes testing for appearance, identity, assay, functional score, uniformity of dosage units, loss on drying, disintegration, dissolution, degradation products, (b) (4). The drug product was tested for total aerobic microbial count (TAMC), total combined yeast and mold count (TYMC), and absence of specific microorganisms such as E. Coli per USP<61 and USP<62>. The applicant will not test for microbial limits testing for release, but perform this test for stability batches. The applicant proposed acceptance criterion of NMT (b) (4)% for the newly identified degradant (b) (4) (b) (4). The applicant tested several batches of the listed product and the product marketed in Europe (Hydrea) and detected up to (b) (4)% of this impurity. In response to an IR, the applicant tightened the acceptance criterion of this impurity to NMT (b) (4)% and updated the acceptance limit for total degradation products to NMT (b) (4)%. The revised limit of (b) (4) (b) (4) was found acceptable by the Pharm-Tox reviewer. The applicant has provided testing result of breakability of engraved Siklos 1000 mg film-coated tablets manufactured by (b) (4) (batch # 60809). The result is acceptable. The applicant has committed that the data for the assessment of breakability of engraved Siklos 1000 mg tablets close to the shelf-life will be provided to the FDA in the annual report or upon FDA request.

The drug product is packaged in HDPL bottles (60 tablets in 15 mL bottles for 100 mg tablets and 30 tablets in 75 mL bottles for 1000 mg tablets). Based on the stability data provided in the submission, the proposed expiry dating period of 36 months is acceptable when stored in the proposed container closure under long term storage conditions of 25°C (b) (4) %RH.

The applicant claimed categorical exclusion from environmental assessment per 21 CFR 25.31(b).

The drug product manufacturing site (b) (4) and the testing site (b) (4) were found acceptable based on profile.

The proposed in vitro dissolution method and the revised acceptance criterion for the proposed drug product have been assessed and seem acceptable, pending the Applicant's justification of the use of (b) (4) rpm as paddle speed. The proposed disintegration method and the revised acceptance criterion for the proposed drug product have been assessed and found acceptable.

(b) (4)

The Office of Product Quality recommended a complete response for this application.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology/toxicology review by Drs. Thompson and Sheth.

The Applicant is relying on published nonclinical data and the FDA's previous findings of safety and effectiveness for Droxia®. The Applicant has not submitted any new nonclinical studies in support of the NDA approval for hydroxyurea, 100 and 1000 mg tablets. The nonclinical section (Module 4) only has literature references. The NDA submission emphasizes findings from an expert panel report published in 2007 by Liebelt, et al. titled "NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea". This report, and other literature in the submission, adequately addresses Pharmacology/Toxicology concerns from the pre- NDA meeting on December 11, 2014.

Pharmacology/Toxicology was consulted by CMC regarding a newly identified degradation product. Based on qualification by use, Pharmacology/Toxicology has no concerns with the degradation product (b) (4).

The Division of Hematology and Oncology Toxicology determined that hydroxyurea (Siklos®) could be approved for the proposed indication.

5. Clinical Pharmacology

Refer to the Clinical Pharmacology Review by Drs. Shen and Habtemariam. Their review states that the NDA is approvable from a clinical pharmacology perspective.

The Applicant submitted a bioequivalence study (Study OTL-001-01) that was not able to be interpreted due to the lack of bioanalytical report and bioanalytical raw data. (b) (4)

The limitations of the data in Study OTL-001-01 also pertained to the PK data. The clinical pharmacology team noted that exploratory analysis suggested that the PK profiles and parameters of Siklos® tablets at steady state are similar between pediatric and adult subjects. Additionally the pediatric PK data from Siklos® was similar to results in the literature from other hydroxyurea formulations. The OCP Team concluded that overall, the PK, efficacy and safety characteristics of Siklos ® in pediatric patients with SCD supported the recommended dosing regimen.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Statistical Review

Trial Design

ESCORT-HU is a multicenter, prospective, observational, cohort study in patients older than 2 years with SCD treated with Siklos® and followed-up for up to 10 years. Clinical and biological efficacy was evaluated to provide supportive data for the NDA submission to support market registration in the US for Siklos® in the pediatric population.

Primary Efficacy Endpoint:

- Absolute change in fetal hemoglobin (HbF) level at least 6 months after initiation of Siklos® as compared to HbF level before initiation of Siklos®.

Major Secondary Efficacy Endpoints:

1. Major Biological Efficacy Endpoints:
   - Absolute change in Hb level at least 6 months after initiation of Siklos® as compared to Hb level before initiation of Siklos®.
   - Absolute change in Hb level at 12 ± 2 months after initiation of Siklos® as compared to Hb level before initiation of Siklos®.
2. Major Clinical Efficacy Endpoints:
   - Proportion of patients with painful crises > 48 hours during the first year of treatment with Siklos®.
   - Absolute change in number of painful crises > 48 hours during the first year of treatment with Siklos® as compared to number of painful crises > 48 hours in the 12 months before initiation of Siklos®.
   - Proportion of patients with episodes of ACS during the first year of treatment with Siklos®.
   - Absolute change in number of episodes of ACS during the first year of treatment with Siklos® as compared to number of episodes of ACS in the 12 months before initiation of Siklos®.
   - Proportion of patients with hospitalizations related to SCD during the first year of treatment with Siklos®.
   - Absolute change in number of hospitalizations related to SCD during the first year of treatment with Siklos® as compared to number of hospitalizations related to SCD in the 12 months before initiation of Siklos®.
   - Absolute change in number of days of hospitalizations related to SCD during the first year of treatment with Siklos® as compared to number of days of hospitalizations related to SCD in the 12 months before initiation of Siklos®.
   - Proportion of patients with blood transfusions during the first year of treatment with Siklos®.

Analysis Population

Efficacy set: The primary efficacy population was the efficacy set defined as patients who were not previously treated with HU, had at least 12 months follow-up, and had data allowing for biological or clinical efficacy evaluations.

Safety set: The primary safety population was the safety set defined as patients who were not previously treated with HU.

Trial Results

Overall, 992 patients were enrolled in the ESCORT-HU study. Of these, 405 of them were less than 18 years old at the time of HU initiation and were included in the Global Safety Set. Among them, 233 patients were not previously treated with HU prior to enrolment and were included in the Safety Set. A follow-up of at least 12 months and data allowing biological or clinical efficacy evaluations were available for 141 subjects.

The data cutoff was February 5, 2016. All patients in the efficacy set have at least 12 months of follow-up and available data for clinical and/or efficacy evaluation. Among them, 66 (46.8%) patients were male and 75 (53.2%) patients were female. Patient age ranged from 1 to 18 years. The mean (± SD) age was 8.08 ± 3.88 years, and 72.7% of patients were aged between 2 and 10 years. Race information was not collected because of EU regulations.

Median (range) fetal hemoglobin (HbF) percentages were 5.6% (1.3,15.0) at baseline and 12.8% (2.1, 37.2) at least 6 months after initiation of Siklos® treatment, with median (range) change of 5.9% (-2.2, 34.7) in 47 patients, and with improvement in 44 out of 47 (93.6%) patients. Median (range) hemoglobin (Hb) levels were 8.2 g/dL (3.7, 14.2) at baseline, 8.8 g/dL (0.7, 13.1) at 6 months, and 8.9 g/dL (5.5,13.2) at 12 months after initiation of Siklos® treatment. The median (range) changes were 0.5 g/dL (-4.6, 6.1) in 63 patients at 6 months and 0.7 g/dL (-6.4, 6.0) in 83 patients at 12 months after initiation of Siklos® treatment. In total, 73 out of 83 (88.0%) patients had improvement in hemoglobin levels at 12 months after initiation of Siklos® treatment.

The results also demonstrate changes in clinical events related to sickle cell disease. When compared to the value during the 12 months prior to treatment initiation, after 12 months of treatment, there was an overall decrease in the number of subjects who experienced at least one painful crisis lasting >48 hours (from 69.2% to 42.5%), a decrease in the incidence of acute chest syndrome (from 23.6% to 5.7%), a decrease in the percentage of patients who had at least one hospitalization related to SCD (from 75.5% to 41.8%), and a decrease in the number of patients requiring transfusion (from 45.9% to 23%). However, due to concerns regarding data capture, missing data and too many zero events, the magnitude of the treatment effect is unclear.

8. Safety

Source: *Combined Clinical/Statistical Review*

The safety profile of Siklos® in pediatric patients with SCD is based on data from the pivotal study, ESCORT-HU, conducted in patients 2 years of age and older, as well as supportive data from published clinical studies using hydroxyurea in pediatric patients with SCD.

ESCORT-HU
At the time of data cut-off (February 5, 2016), a total of 992 subjects were enrolled. Of these, 405 subjects were less than 18 years of age at the time of Siklos® initiation and were included in the global pediatric safety set. Among them, 233 subjects were not previously treated with hydroxyurea at the time of Siklos® initiation and are included in the Safety Set (SS).

A summary of the key safety findings are listed below:

- The Siklos® starting dose was 15 mg/kg orally once daily. The dose could be increased, as tolerated, by 5 mg/kg/day every 8 weeks or if a crisis occurred, until a maximum tolerated dose or 35 mg/kg/day was reached.
- In total, 63 (15.6%) subjects in the Global Safety Set and 36 (15.5%) subjects in the Safety Set had a dose reduction due to adverse reactions or lab abnormalities. No subjects discontinued study drug due to an adverse event.
- Serious treatment-emergent adverse reactions (including both sickle-cell related events and non-sickle cell related events) were reported in 109 (26.9%) subjects in the global safety set and 63 (27.0%) subjects in the safety set.
- The most frequent non-sickle cell related serious adverse reactions in the global safety set were infections (18.0%), thrombocytopenia (3.7%) and neutropenia (3.0%).
- Additional safety issues have been identified with the use of hydroxyurea include: myelosuppression, skin and subcutaneous tissue disorders, carcinogenicity and teratogenicity.
- In the ESCORT-HU study, there was 1 death in a pediatric patient. This event was considered to be not related to Siklos® treatment.

Published Controlled Studies: Overview of Safety Results
The safety profile of hydroxyurea for the treatment of adults with SCD is well established, and many studies of hydroxyurea in pediatric patients with SCD have been reported in the literature. The BABY HUG, SWiTCH and TWiTCH studies reported safety data. Details of adverse events were not reported in the other two published controlled studies.

Across the 5 studies, no adverse events leading to treatment withdrawal were reported and there were no adverse events that were not related to underlying sickle cell disease that resulted in death.

Overall, the safety findings in the published controlled studies are consistent with the safety profile of Siklos® in ESCORT-HU with regards to the most frequent drug-related adverse events, i.e. blood and lymphatic disorders (neutropenia, especially in the youngest children [as seen in BABY HUG], as well as anemia, reticulocytopenia and thrombocytopenia [as seen in

the SWiTCH study]), infections, gastrointestinal disorders and skin and subcutaneous tissue disorders (reported in Jain et al. 2012 and the BABY HUG studies).

9. Advisory Committee Meeting

This application was not presented to the Oncologic Drug Advisory Committee.

10. Pediatrics

This application sought only a pediatric indication. A Written Request was not issued for this product. The following was communicated to the Applicant in the Type C Guidance meeting held on June 14, 2016:

> Siklos has been granted orphan drug designation for the treatment of sickle cell disease in patients under 18 years of age. If you are the first sponsor to receive marketing approval for hydroxyurea for the above orphan designation indication, you are eligible for orphan exclusivity for the approved indication.
>
> Pediatric Exclusivity is separate from Orphan Drug Exclusivity. Pediatric Exclusivity adds 6 months to existing Patents/Exclusivity. Pediatric Exclusivity is granted in response to a Written Request (WR). If you want to be considered for Pediatric Exclusivity, you should submit a Proposed Pediatric Study Request (PPSR) to the IND prior to submission of the NDA. FDA will consider issuing a WR in response to the PPSR. FDA cannot issue a WR for a study that has been submitted to the FDA. See Guidance for Industry Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act.

The Applicant did not submit a PPSR prior to submission of the NDA.

All other relevant pediatric discussions are contained within the other review sections.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Financial disclosures:** In accordance with 21 CFR 54, the Applicant submitted financial disclosure information for investigators. There were no investigators from study ESCORT-HU who reported financial interest of arrangements.
- **Other GCP issues:** None
- **OSI audits:** OSI audits were not requested for the clinical sites.

12. Labeling

Labeling negotiations with the sponsor were ongoing when it was determined that the Applicant's request (b) (4) was denied. DMEPA, DMPP, OPDP and the

Division's Associate Director for Labeling participated in labeling discussions and provided recommendations.

A major ongoing issue at the time labeling negotiations were ceased was the instruction to use gloves when handling Siklos®. The Applicant was of the opinion that gloves were not necessary. Given that Siklos® is an antineoplastic, the FDA felt strongly that the prescribing information and patient information should contain information instructing individuals handling Siklos® or bottles of Siklos® to wear disposable gloves. Additionally, the Instructions for Use document should be revised to include images of gloved hands during preparation.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Complete Response

- Risk Benefit Assessment

  The efficacy and safety results of the ESCORT-HU study demonstrate an acceptable benefit-risk profile for Siklos® for the proposed indication, "to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises". The Clinical, Statistics, Clinical Pharmacology and Pharmacology/toxicology teams all deemed that this application was approvable for the proposed indication. However, the Office of Product Quality recommends a complete response. Furthermore, the other discipline reviews rely in part on results provided in published literature and the Agency's previous findings of safety and effectiveness for Droxia®. (b) (4) t is recommended that this application receive a complete response.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Not applicable

- Recommendation for other Postmarketing Requirements and Commitments

  Not applicable

- Recommended Comments to Applicant

  (b) (4)

(b) (4)

References:

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2. GREEN N. S., BARRAL S. Emerging science of hydroxyurea therapy for pediatric sickle cell disease, Pediatr Res 2014: 75: 196-204.
3. YAWN B. P., BUCHANAN G. R., AFENYI-ANNAN A. N., BALLAS S. K., HASSELL K. L., JAMES A. H. et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members, JAMA 2014: 312: 1033-1048.

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/s/

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02/07/2017