CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208843
Submission Date	06/30/2017
Submission Type	505(b)(2)
Brand Name	Siklos
Generic Name	Hydroxyurea
Dosage Form and Strength	100 mg and triple functionally scored 1000 mg, film-coated tablets
Route of Administration	Oral
Proposed Indication	To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises.
Applicant	Addmedica SAS
OCP Review Team	Guoxiang Shen, Ph.D. and Bahru Habtemariam, Pharm.D.
OCP Final Signatory	Bahru Habtemariam, Pharm.D.

EXECUTIVE SUMMARY

Hydroxyurea has been approved and marketed as Hydrea® and Droxia® for oncology and sickle cell indications, respectively, for several decades. Addmedica SAS seeks to extend the sickle cell indication to children ages 2 and older under the 505(b)(2) pathway.

The original 505(b)(2) application was submitted on 07/29/2016 for hydroxyurea supplied as 100 mg tablets and triple functionally scored 1000 mg tablets in order to allow flexible pediatric dosing. At that time, due to major deficiencies identified (b) (4) a Complete Response (CR) letter was issued by the FDA on 02/09/2017.

This is a resubmission to address the deficiencies identified in the CR letter. The resubmission contains no new clinical pharmacology information for review. The NDA is approvable from a clinical pharmacology perspective as stated in the original clinical pharmacology review (see review detail in DARRTS dated 01/10/2017, also see the attached original review in Appendix). This memo finalizes our review of this NDA.

Appendix: Original clinical pharmacology review for NDA208843 (01/10/2017)

APPEARS THIS WAY ON ORIGINAL

Office of Clinical Pharmacology Review

NDA Number	208843
Submission Date	07/29/2016
Submission Type	505(b)(2)
Brand Name	SIKLOS
Generic Name	Hydroxyurea
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Route of Administration	Oral
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.
Applicant	Addmedica SAS
OCP Review Team	Guoxiang Shen, Ph.D. and Bahru Habtemariam, Pharm.D.
OCP Final Signatory	Bahru Habtemariam, Pharm.D.

1. EXECUTIVE SUMMARY

Hydroxyurea has been approved and marketed as Hydrea® and Droxia® for adult oncology and sickle cell indications, respectively, for several decades. Addmedica SAS seeks to extend the sickle cell indication to children ages 2 and older under the 505(b)(2) pathway.

To support the 505(b)(2) application, the applicant developed proprietary formulation where hydroxyurea is supplied as 100 mg tablets and triple functionally scored 1000 mg tablets in order to allow flexible pediatric dosing.

The applicant conducted a bioequivalence (BE) PK study and a clinical registry study in children with sickle cell disease (SCD). The review team deemed the BE results in the PK study that was conducted 12 years ago uninterpretable due to the lack of bioanalytical report and bioanalytical raw data. (b) (4)

The clinical registry study was conducted in children with SCD ages 2-18 (N=405). The primary endpoint was change in hemoglobin F levels at least 6 months after initiation of Siklos treatment with a starting dose of 20 mg/kg. The median hemoglobin F levels increased from 5.6% at baseline to 12.8% after 6 months treatment with Siklos at the recommended dose. In terms of safety, the most frequently reported adverse reaction in this study was myelosuppression with mild to moderate neutropenia as the most common manifestation.

Overall, the PK, efficacy and safety characteristics of Siklos in pediatric patients with SCD support the approval of Siklos at recommended dosing regimen.

1.1 Recommendations

The Office of Clinical Pharmacology's Division of Clinical Pharmacology V has reviewed this 505(b)(2) NDA. The NDA is approvable from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The applicant didn't conduct any clinical pharmacology studies except the Phase 1 PK trial OTL-001-01. Refer to the approved labeling of Droxia® for details of the clinical pharmacology and PK characteristics of hydroxyurea.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Siklos is available as 100 mg tablets and triple functionally scored 1000 mg tablets, allowing the dosing of Siklos in 100 and 250 mg increments.

- 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 an 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.

2.3 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts in the final package insert:

- Revise the clinical pharmacology related sections throughout the labeling to be consistent with approved Droxia® labeling.
- Delete Section (b) (4)
- In Section 12.3 (Pharmacokinetics), under "Special Populations", a statement indicating PK of hydroxyurea is similar between children (ages 4 to (b) (4)) and adults was added for children.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Clinical Pharmacology Questions

3.1.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. Biological and clinical efficacy of Siklos have been assessed in 405 pediatric patients with sickle cell disease from 2-18 years of age, of which 141 had not been previously treated with hydroxyurea prior to enrollment in the European registry study ESCORT-HU. The median (range) hemoglobin F 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 the recommended dosing regimen. The median (range) change of hemoglobin levels 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 addition, treatment with Siklos showed improvement in the rates of vaso-occlusive events, acute chest syndrome, hospitalization and blood transfusion after 12 months of treatment among previously untreated pediatric patients (N=141) (see **Table 1**).

Table 1. Summary of SCD related events in previously untreated pediatric patients (N=141) before and after Siklos treatment

SCD events	Number (%) Patients with the event	
	In the 12 months prior to enrollment	After 12 months of treatment
At least one vaso-occlusive episode (in 120 evaluable patients)	83 (69.2%)	51(42.5%)
At least one episode of acute chest syndrome (in 123 evaluable patients)	29 (23.6%)	7 (5.7%)
At least one hospitalization due to SCD (in 110 evaluable patients)	83 (75.5%)	46 (41.8%)
At least one blood transfusion (in 122 evaluable patients)	56 (45.9%)	28 (23.0%)

3.1.2 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Children

In the Phase 1 PK/BE trial OTL-001-01, PK of hydroxyurea from Siklos 1000 mg tablets and Hydrea 500 mg capsules in pediatric and adult patients with SCD were assessed in pseudo steady

state conditions, i.e. patients had taken Hydrea capsules for at least three months prior to inclusion (one month on a stable dose) and provided the critical PK data for Siklos at 15 to 25 mg/kg/day after 14 days of dosing in pediatric patients.

While the issue related to missing bioanalytical raw data also applies to the pediatric PK data, exploratory analysis suggests that PK profiles and parameters of hydroxyurea at steady state from Siklos tablets are similar between pediatric and adult patients with SCD (see **Figure 1** and **Table 2**).

Figure 1. Mean concentrations (SD) versus time of hydroxyurea in 11 pediatrics (circle) and 15 adult (squares) patients with SCD receiving Siklos tablets

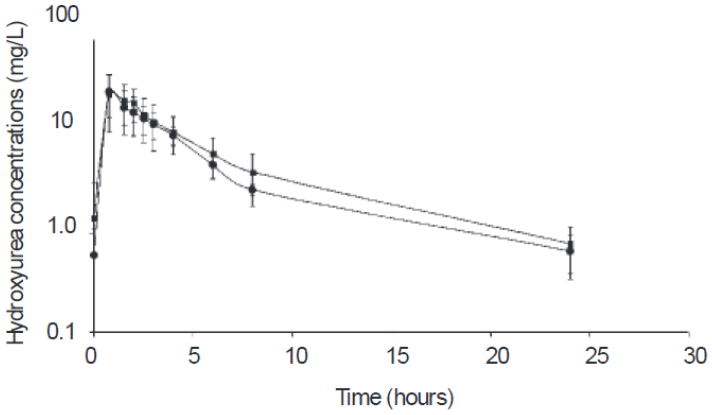

Table 2. Summary of hydroxyurea PK parameters (mean ± SD) in pediatric and adult patients receiving Siklos tablets

PK parameters	Pediatrics (N=11)	Adults (N=15)
Dose, mg/kg	21.37	20.83
Cmax, mg/L	29.61 ± 11.60	29.47 ± 13.16
Cmin, mg/L	1.09 ± 1.49	0.85 ± 0.37
AUC_{0-24}, mg/L*h	124.2 ± 55.0	135.4± 53.9
CL/F, L/h	7.25 ± 4.58	9.89 ± 2.37
$T_{1/2}$, h	7.49 ± 3.34	6.27 ± 1.54

In addition, the pediatric PK data of Siklos in Phase 1 trial OTL-001-01 are further compared with PK data of hydroxyurea in pediatric patients from other formulations published in the literature. As shown in **Table 3**, Cmax of hydroxyurea in the OTL-001-01 (Siklos) trial was slightly lower than that in the study published by Estepp *et al* [1], which can be explained by differences in the PK sampling schedule: the Estepp study started sampling at 15 minutes post dose compared to study OTL-001-01 where the first PK sample was collected at 45 minutes post dose. The AUC of hydroxyurea from OTL-001-01 (Siklos) trial is slightly higher than those published in the literature, which may be explained by a more extensive PK sampling (24 hours) in the Siklos trial than that (8 hours) in other studies. In summary, pediatric PK of hydroxyurea

from Siklos tablets are generally consistent with that published in the literature [1, 2]. Therefore, the comparative (adult vs. pediatric) PK evaluation conducted in the current applicant is consistent with published information and supports the applicant's claim that the PK properties of hydroxyurea are similar in adults and children.

Table 3. Comparison of PK parameters (mean ± SD) of hydroxyurea in pediatrics between Study OTL-001-01 and studies in the literature

Study	Cohort(N)	Age	Dose, mg/kg	Form	Cmax, µg/mL	AUC_{inf}, µg*h/mL	CL/F, L/h/kg
OTL-001-01	pediatric (N=11)	10.1±5.7	21.4	tablet	29.6±11.6	124.2±55.0	0.20±0.07
Estepp *et al* [1]	1 (N=17)	4.5±1.7	22.7	liquid	37.4±9.3	104.5±18.8	0.23±0.03
	2 (N=22)	12.0±3.6	21.7	liquid	34.0±8.7	111.9±29.4	0.21±0.04
	2 (N=22)	12.0±3.6	22.6	capsule	33.6±8.2	116.3±30.0	0.20±0.03
Ware *et al* [2]	Pediatric (N=87)	9.6±4.8	20	liquid	26.1±6.8	93.0±23.4	0.24±0.09

The safety of Siklos has been specifically assessed in study ESCORT-HU. The most frequently reported adverse reaction in ESCORT-HU was myelosuppression with mild to moderate neutropenia as the most common manifestation. Other adverse reactions include skin and subcutaneous disorders (skin depigmentation/melanonychia, skin rash, and alopecia), nausea, headache. The most frequent serious adverse events were neutropenia (6.9%) and thrombocytopenia (2.7%).

Overall, the PK, efficacy and safety characteristics of Siklos in pediatric patients with SCD support the recommended dosing regimen.

References:

1. Estepp, JH. *et al* Pharmacokinetics and Bioequivalence of a Liquid Formulation of Hydroxyurea in Children With Sickle Cell Anemia *J Clin Pharmacol. 2016 Mar;56(3):298-306*
2. Ware RE *et al* Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia *Blood. 2011 Nov 3;118(18):4985-91*

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/s/

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10/06/2017

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10/10/2017