CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***APPROVAL***

NDA 208843
Review 2

Drug Name/Dosage Form	Siklos (hydroxyurea) film coated tablets
Strength	100 mg and 1000 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Addmedica SAS
US agent, if applicable	David Lucking, Voisin Consulting Inc. Life Sciences

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA submission(SD#1)	*07/29/2016*	All CMC (Original Submission)
Amendments (SD#19)	06/30/2017	Biopharm, DP (Resubmission)
Amendments (SD#20)	11/13/2017	DP (labeling)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rohit Tiwari	CDER/OPQ/ONDP/DNDAPI
Drug Product	Xing Wang	OMPT/CDER/OPQ/ONDP/DNDPI/ NDPBII
Process	Quamrul Majumder	CDER/OPQ/OPF/DPAI/B2
Microbiology	-	
Facility	Laura Fontan	CDER/OPQ/OPF/DPAI/B2
Biopharmaceutics	Mei Ou	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Laiq	CDER/OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	OMPT/CDER/OPQ/ONDP/DNDPI/ NDPBII
Laboratory (OTR)	-	
ORA Lead	-	
Environmental Analysis (EA)	-	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Drug Substance: Hydroxyurea	Active	March 9, 2017	Adequate
	Type III *(if applicable)*			Active		Adequate per MAPP 5015.5 (Rev. 1)
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

None

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

From the CMC perspective, NDA 208843, for Siklos® 1000 mg and 100 mg tablets, is recommended for APPROVAL.

II. Summary of Quality Assessments

A. Product Overview

NDA 208843 is submitted under section 505(b)(2) in support of the use of Siklos (hydroxyurea) 100 mg and 1000 mg film coated tablets 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 (SCA) with recurrent moderate to severe painful crises. It was designated by the Agency as an orphan product for the treatment of sickle cell disease (SCD) in patients under 18 years on 23 July, 2013 (Designation # 13 4004).
On 06/30/2017, the Applicant filed a Class 2 Resubmission of NDA 208843 for Hydroxyurea Tablets. The resubmission includes the Applicant's responses to the deficiencies listed in the FDA CR letter; (b) (4) ***Question Based Approach document and additional dissolution data.***

Proposed Indication(s) including Intended Patient Population	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 (SCA) with recurrent moderate to severe painful crises.
Duration of Treatment	NA
Maximum Daily Dose	35 mg/kg/day
Alternative Methods of Administration	NA

B. Quality Assessment Overview

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 last reviewed by Dr. Rohit Tiwari on March 09, 2017 and was found to be adequate. No quality amendment has since been submitted to this DMF. No additional drug substance data was provided in the NDA resubmission. 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)). No additional facility issue has been identified.

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 additional facility issue is identified for the drug product manufacturing or testing sites.
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. No novel excipients or excipients with human or animal origin are used. The drug product manufacturing process includes (b) (4) The applicant provided new dissolution data to support the approval of the revised dissolution method with a paddle rotation speed of 50 rpm.
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 (b) (4) RH.

The overall *in vitro* dissolution data fully demonstrated that the listed drug product and the proposed Hydroxyurea Tablets (both strengths) are very rapidly dissolving (> (b) (4)% in 15 min). The provided solubility information/data fully support hydroxyurea as a highly soluble drug substance over the physiologic pH range. The drug product does not contain any excipients that will affect the rate or extent of absorption of the drug. The *in vivo* human pharmacokinetic information provided in the submission and from scientific literature showed that the bioavailability of hydroxyurea is very high and there are no reports of bioavailability problems, indicating that hydroxyurea is a highly permeable

drug *in vivo*. As per 21 CFR 320.24(b)(5/6), the overall *in vitro* and *in vivo* information/data provided by the Applicant are deemed adequate and acceptable to establish the scientific bridge between the listed drug product, Droxia® (hydroxyurea) Capsules and the proposed Hydroxyurea Tablets.

The PI and carton container label is currently being discussed with the applicant.

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

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

Anamitro Banerjee

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BIOPHARMACEUTICS

Application No.:	**NDA 208843-ORIG-1-RESUB-19/505(b)(2)**
Applicant:	**Addmedica SAS**
Product Name/Strengths:	**Siklos® (hydroxyurea) Tablets, 100 mg and 1000 mg**,
Primary Reviewer	**Mei Ou, Ph.D.**
Secondary Reviewer:	**Okpo Eradiri, Ph.D.**
Tertiary Reviewer:	**Angelica Dorantes, Ph.D.**
RECOMMENDATION:	**ADEQUATE**

Review Summary:

Background: In the original NDA submission dated 07/29/2016, the Applicant submitted (b) (4) the NDA received a Complete Response (CR) action because (b) (4) support approval could not be granted.

Submission: On 06/30/2017, the Applicant filed a Class 2 Resubmission of NDA 208843 for Hydroxyurea Tablets. The resubmission includes the Applicant's responses to the deficiencies listed in the FDA CR letter; (b) (4) and additional dissolution data.

Drug Product: The proposed drug product, **Siklos® (hydroxyurea) 100 and 1000 mg tablets**, is an antineoplastic agent, indicated 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. It is noted that there is a medically urgent need for the proposed hydroxyurea tablets for the treatment of sickle cell disease in children.

Review: The focus of the Biopharmaceutics review was to evaluate the submitted information/ data and provide a recommendation on the acceptability of the following:

- (b) (4)
- Overall formulation, *in vitro* and *in vivo* information/data supporting the bridge between the listed drug product, Droxia® (hydroxyurea) Capsules [NDA 016295 held by Bristol Myers Squibb (BMS)] and the proposed Hydroxyurea Tablets product.
- New dissolution data supporting revised dissolution method.

Reviewer's Assessment:

(b) (4)

Dissolution: Both strengths of the proposed drug product were demonstrated to be very rapidly dissolving (> (b) (4) % in 15 min). The provided new dissolution data support the approval of the revised dissolution method with a paddle rotation speed of 50 rpm.

Information Supporting Bridging:
The overall *in vitro* dissolution data fully demonstrated that the listed drug product and the proposed Hydroxyurea Tablets are very rapidly dissolving. The provided solubility information/data fully support hydroxyurea as a highly soluble drug substance over the physiologic pH range. The drug product does not contain any excipients that will affect the rate or extent of absorption of the drug. The *in vivo* human pharmacokinetic information provided in the submission and from scientific literature showed that the bioavailability of hydroxyurea is very high and there are no reports of bioavailability problems, indicating that that hydroxyurea is a highly permeable drug *in vivo*.

RECOMMENDATION

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 320.24(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 1000 mg tablets.

Primary Biopharmaceutics Reviewer Name and Date:

Mei Ou, Ph.D. 10/30/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics (DBP)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Secondary Reviewer Name and Date:

Okpo Eradiri, Ph.D. 10/31/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics (DBP)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Tertiary Biopharmaceutics Reviewer Name and Date:

Angelica Dorantes, Ph.D. 10/31/2017
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics (DBP)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Biopharmaceutics Assessment – Reviewer Notes

- **List of Submissions being reviewed (table):**

06/30/2017	Class 2 Resubmission of NDA 208843 (eCTD-0018)

- ***Drug Product:***

The proposed hydroxyurea tablets have two strengths, 100 mg and 1000 mg tablets. The 1000 mg tablet has 3 score lines so that it can be divided into four equal parts. The drug substance, hydroxyurea (USP), has a molecular weight of 76.1 g/mol. The molecular structure is given in figure 1 below.

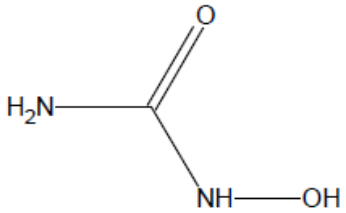

Figure 1: Molecular structure of hydroxyurea

The dissociation constant (pKa) is 10.6. *Hydroxyurea has no observed stereochemistry or polymorphism, also contains three ionizable protons and behaves as a weak acid (Kofod H et al., 1954).*

The qualitative and quantitative composition of the proposed drug product, Siklos® 100 mg and 1000 mg tablets, are presented in table 1 below.

Table 1: Quantitative composition of the proposed hydroxyurea tablets, 100 mg and 1000 mg

Component	Centesimal composition (%w/w)	Quantity per 100 mg tablet (mg)	Quantity per 1000 mg tablet (mg)	Function	Reference to quality Standard
Hydroxycarbamide	71.25	100.000	1000.000	Drug substance	USP-NF current ed., Ph. Eur. current ed.
Silicified microcrystalline cellulose (b) (4)	(b) (4)				USP-NF current ed.
Sodium stearyl fumarate (b) (4)					USP-NF current ed., Ph. Eur. current ed.
Amino methacrylate copolymer (b) (4)					USP-NF current ed., Ph. Eur. current ed.
					USP-NF current ed., Ph. Eur. current ed.
Total film-coated tablets		**141.640**	**1416.403**		

(b) (4)

- **Complete Response Deficiencies**

The Complete Response letter dated 02/09/2017 (uploaded in *DARRTS*), included the following Biopharmaceutics/Clinical Pharmacology deficiencies:

(b) (4)

[redacted]

4. Regarding the proposed dissolution method, we recognize that you adopted the USP dissolution method for Hydroxyurea Tablets. However, include in your resubmission, a justification for the paddle speed of (b) (4) rpm by comparing dissolution profiles obtained with paddle speeds of 50 (b) (4) rpm. If the results indicate similar dissolution profiles, implement 50 rpm as the paddle speed for the dissolution test of your drug product.

➢ **Resubmission:**

The Class 2 Resubmission of NDA 208843included the following:

- (b) (4)
- Additional dissolution data using the recommended 50 rpm paddle speed (refer to M.1.11.4 of 06/30/2017 resubmission, Application 208843 - Sequence 0018 - Response to Complete Response Letter dated February 9, 2014; and the M.1.12.15 of 06/30/2017 resubmission, Application 208843 - Sequence 0018 - (b) (4)

➢ **Review:**

The focus of the Biopharmaceutics review was; **1)** the evaluation of the Applicant's responses to the deficiency comments included in the CR letter (b) (4) **2)** additional dissolution data, and **3)** overall *in vitro* and *in vivo* information/data supporting the scientific bridge between the listed and proposed drug products.

Reviewer's Evaluation of Applicant's Responses to CR Deficiencies

(b) (4)

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(b) (4)

[redacted]

- ***Dissolution Test:***

In order to justify the paddle speed of (b) (4) rpm proposed in the original submission, the Applicant submitted additional comparative dissolution profile data @ (b) (4) 50 rpm (M.1.11.4 and M.3.2.P.2.2.3.2.5). The dissolution testing conditions are listed in table 12. The batches used for method optimization are summarized in table 13. The summarized dissolution data and mean dissolution profiles are presented in table 14 and figures 2-3.

Table 12: Original and Revised Dissolution Tests for Siklos (hydroxyurea) 100 and 1000 mg Tablets

	Original submission (07/29/2016)	**Resubmission (06/30/2017)**
USP Apparatus	II (Paddle)	II (Paddle)
Dissolution Medium	Demineralized water	Demineralized water
Volume	500 mL (Siklos 100 mg tablet); 1000 mL (Siklos 1000 mg tablet and ¼ split portions of Siklos 1000 mg tablet)	500 mL (Siklos 100 mg tablet); 1000 mL (Siklos 1000 mg tablet and ¼ split portions of Siklos 1000 mg tablet)
Rotation Speed	(b) (4) **rpm**	**50 rpm**
Temperature	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Points	5, 10, 15, and 30 minutes	5, 10, 15, and 30 minutes
Acceptance Criterion	Q= (b) (4) % in 15 minutes	Q= (b) (4) % in 15 minutes

Table 13: Siklos batches used in the paddle speed study (from M.3.2.P.2 of 06/30/2017 resubmission)

Product	Manufacturer	Batch number	Manufacturing date
Siklos 100 mg tablet	(b) (4)	52021	30 Jun 2015
Siklos 1000 mg tablet		60809	20 Oct 2016

Table 14: Dissolution data of Siklos tablets used in the paddle speed study

Product	Batch No.	Rotation speed	Mean dissolution % (min-max%, RSD%) (n=12 units)			
			5 min	10 min	15 min	30 min
100 tablet	52021	(b) (4)				
		50 rpm	97.43 (94.27-100.17, 2.0)	97.97 (94.72-101.06, 2.0)	97.75 (94.10-100.03, 2.1)	97.35 (93.81-99.83, 2.0)
1000 tablet	60809	(b) (4)				
		50 rpm	98.67 (97.17-100.05, 1.0)	99.00 (97.57-100.12, 0.9)	99.30 (97.52-100.48, 1.1)	99.92 (98.37-101.18, 1.0)

Figure 2: Overlay of dissolution profile in water acquired at 50 (b) (4) rpm For Siklos 100 mg tablets

(b) (4)

Figure 3: Overlay of dissolution profile in water acquired at 50 (b) (4) rpm For Siklos 1000 mg tablets

(b) (4)

The approved method and acceptance criterion for the dissolution test are presented below.

FDA's approved dissolution method and acceptance criterion for the proposed drug product, Siklos® (hydroxyurea) 100 mg and 1000 mg tablets

USP Apparatus	II (Paddle)
Dissolution Medium	Demineralized water
Volume	500 mL (Siklos 100 mg tablets); 1000 mL (Siklos 1000 mg tablets and ¼ split portions of Siklos 1000 mg tablets)
Agitation speed	**50 rpm**
Temperature	37°C ± 0.5°C
Sampling time points	5, 10, 15, and 30 minutes
Acceptance Criterion	**Q= (b) (4) % in 15 minutes**

Reviewer's Assessment:

As presented in table 14 and figures 2-3, Siklos 1000 mg and 100 mg tablets demonstrated to be rapidly dissolving with more than (b) (4) % of drug dissolved within 15 minutes @ (b) (4) 50 rpm rotation speeds. It is noted that the Applicant accepted and implemented the revised 50 rpm paddle speed for the dissolution test of Siklos® (hydroxyurea) 100 mg and 1000 mg tablets at batch release and on stability. The dissolution analytical procedure is confirmed to be updated accordingly in Module 3.2.P.5.2. The revised dissolution method and acceptance criterion have been confirmed in M.3.2.P.5.1 and M.3.2.P.5.2.

(b) (4)

- **Data Supporting Bridging of Listed and Proposed Drug Products**

The overall *in vitro* dissolution data fully demonstrated that the listed drug product and the proposed Hydroxyurea Tablets are very rapidly dissolving (> (b) (4) % in 15 min). The provided solubility information/data fully support hydroxyurea as a highly soluble drug substance over the physiologic pH range. The formulation of the drug product does not contain any excipients that will affect the rate or extent of absorption of the drug. The *in vivo* human pharmacokinetic information provided in the submission and from scientific literature showed that the bioavailability of hydroxyurea is very high and there are no reports of bioavailability problems, indicating that that hydroxyurea is a highly permeable drug *in vivo*.

Reviewer's Assessment:
Based on 21 CFR 320.24(b)(5/6), this Reviewer considers that the overall *in vitro* and *in vivo* information/data provided by the Applicant is adequate and acceptable to establish the scientific bridge between the listed drug product, Droxia® (hydroxyurea) Capsules and the proposed Hydroxyurea Tablets.

RECOMMENDATION:

Per 21 CFR 320.24(b)(6), the Division of Biopharmaceutics recommends **APPROVAL** of NDA 208843 for **Siklos® (hydroxyurea) 100 and 1000 mg tablets.**

Mei Ou

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Okponanabofa Eradiri

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Angelica Dorantes

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Functionally Scored Tablets: Content uniformity (based on uneven split)	• Formulation changes on the approved scored tablets • Process parameters • Scale/equipments • Site	L		Acceptable	
Functionally Scored Tablets: Friability	• Formulation and/ on the approved scored tablets • Process parameters • Scale/equipments • Site	L	Firm has provided breakability data of a batch (# 60809) of engraved Siklos 1000 mg film-coated tablets manufactured by (b) (4) (b) (4) The result is acceptable.	Acceptable	On 13-Oct-2016, Addmedica commits that the data for the assessment of breakability close to the shelf-life will be provided to the FDA in the annual report or upon FDA request.
Dissolution – BCS Class I & III	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	The applicant provided adequate in-vivo and dissolution information in the resubmission

Anamitro Banerjee

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Recommendation: ***Complete Response***

NDA 208843
Review 1

Drug Name/Dosage Form	Siklos (hydroxyurea) film coated tablets
Strength	100 mg and 1000 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Addmedica SAS
US agent, if applicable	David Lucking, Voisin Consulting Inc. Life Sciences

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA submission(SD#1)	*07/29/2016*	All CMC
Amendments (SD#5)	09/27/2016	Biopharm, DS
Amendments (SD#6)	*10/19/2016*	*DP*
Amendments (SD#8)	10/25/2016	Process, DP
Amendments (SD#9)	10/31/2016	*Biopharm, Micro*
Amendments (SD#12)	11/17/2016	All CMC
Amendments (SD#13)	11/22/2016	Biopharm
Amendments (SD#14)	11/30/2016	DP (labeling)
Amendments (SD#12)	12/20/2016	Biopharm
Amendments (SD#17)	12/27/2016	DP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rohit Tiwari	CDER/OPQ/ONDP/DNDAPI
Drug Product	Xing Wang	OMPT/CDER/OPQ/ONDP/DNDPI/ NDPBII
Process	Quamrul Majumder	CDER/OPQ/OPF/DPAI/B2
Microbiology	-	
Facility	Laura Fontan	CDER/OPQ/OPF/DPAI/B2
Biopharmaceutics	Mei Ou	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Laiq	CDER/OPQ/OPRO/B1

Application Technical Lead	Anamitro Banerjee	OMPT/CDER/OPQ/ONDP/DNDPI/ NDPBII
Laboratory (OTR)	-	
ORA Lead	-	
Environmental Analysis (EA)	-	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Drug Substance: Hydroxyurea	Active	January 6, 2017	Adequate
	Type III *(if applicable)*			Active		Adequate per MAPP 5015.5 (Rev. 1)
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

None

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

(b) (4)

From the Biopharmaceutics perspective, NDA 208843, for Siklos® 1000 mg and 100 mg tablets, is recommended for a COMPLETE RESPONSE (CR).

II. Summary of Quality Assessments

A. Product Overview

NDA 208843 is submitted under section 505(b)(2) in support of the use of Siklos (hydroxyurea) 100 mg and 1000 mg film coated tablets 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 (SCA) with recurrent moderate to severe painful crises. It was designated by the Agency as an orphan product for the treatment of sickle cell disease (SCD) in patients under 18 years on 23 July, 2013 (Designation # 13 4004).

Proposed Indication(s) including Intended Patient Population	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 (SCA) with recurrent moderate to severe painful crises.
Duration of Treatment	NA
Maximum Daily Dose	35 mg/kg/day
Alternative Methods of Administration	NA

B. Quality Assessment Overview

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) 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) . 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) 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)

From the Biopharmaceutics perspective, NDA 208843, for Siklos® 1000 mg and 100 mg tablets, is recommended for a COMPLETE RESPONSE (CR).

The following deficiency comments should be conveyed to the Applicant in the CR action letter:

(b) (4)

(b) (4)

[redacted]

4. Regarding the proposed dissolution method, we recognize that you adopted the USP dissolution method for Hydroxyurea Tablets. However, include in your resubmission, a justification for the paddle speed of (b) (4) rpm by comparing dissolution profiles obtained with paddle speeds of 50 (b) (4) rpm. If the results indicate similar dissolution profiles, implement 50 rpm as the paddle speed for the dissolution test of your drug product.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

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ENVIRONMENTAL ANALYSIS

R Regional Information

Environmental Analysis

See environmental analysis review in section R of Drug Product Review.

Primary EA Reviewer Name and Date: Xing Wang, Ph.D., 22-Dec-2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D., ONDPI/NDPBII Acting Branch Chief

Anamitro Banerjee

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Date: 12/22/2016 02:51 21PM
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Comments: I concur with Dr. Xing Wang's assessment.

Xing Wang

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CHAPTER IV: Labeling

Package Insert (12/12/2016)

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: SIKLOS Established name: hydroxyurea	Adequate
Dosage form, route of administration	Dosage: (b) (4) Tablet Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 100 mg and triple functional scored 1000 mg tablet	Adequate

Conclusion: The 1000 mg tablet is triple-scored. The comment has been conveyed to the sponsor. Firm has made corrections.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Film-coated tablets:

- 100 mg tablets: off-white round, film-coated tablet embossed 100 on one side.

- 1000 mg tablets: off-white, capsule-shaped, film-coated (b) (4) scoring on both sides which can be divided into four equal parts embossed with "T" on one side. (b) (4)

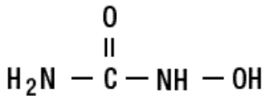
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Film coated tablets	Adequate
Strengths: in metric system	100 mg and 1000 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets (100 mg): off-white round, film-coated tablet embossed 100 on one side Tablets (1000 mg): off-white, capsule-shaped, film-coated (b) (4) triple scoring on both sides	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

SIKLOS is an antimetabolite that is available for oral use as 100 mg film-coated tablet and triple-scored 1,000 mg film-coated tablet containing 100 and 1,000 mg of hydroxyurea, respectively. Inactive ingredients include sodium stearyl fumarate, silicified microcrystalline cellulose, (b) (4) methacrylate copolymer.

Hydroxyurea is a white crystalline powder. It has a molecular weight of 76.05. Its structural formula is:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Same as RLD	Adequate

Conclusion: Adequate

The first sentence is changed to "SIKLOS is an antimetabolite that is available for oral use as 100 mg film-coated tablet and triple-scored 1000 mg film-coated tablet containing 100 and 1000 mg of hydroxyurea, respectively." The comments have been conveyed to the sponsor and firm has made corrections.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 How Supplied

SIKLOS film-coated tablet is supplied in High density polyethylene (HDPE) bottle with polypropylene child-resistant cap with a desiccant unit containing 30 (SIKLOS 1000 mg) or 60 film coated tablets (SIKLOS 100 mg).

SIKLOS is supplied in the following strengths:

- 100 mg off-white round, film-coated tablet, embossed with 100 on one side.

- 1000 mg off-white, capsule-shaped film-coated (b) (4) triple scoring on both sides which can be divided into four equal parts, embossed with "T" on one side. (b) (4)

(b) (4)

	Bottles of 30	Bottles of 60
100 mg	N/A	NDC XXXX-XXXX-XX
1000 mg	NDC XXXX-XXXX-XX	N/A

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep tightly closed.
Broken 1,000 mg tablets must be stored in the bottle and must be used within three months.

16.3 Handling and Disposal
SIKLOS is (b) (4) drug. Follow applicable special handling and disposal procedures [see References (15)].
. Wash hands with soap and water before and after contact with the bottle or tablets when handling SIKLOS. Avoid exposure to crushed tablets. If contact with crushed tablets occurs on the skin, wash affected area immediately and thoroughly with soap and water. If contact with crushed tablets occurs on the eye(s), the affected area should be flushed thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes. (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Provided	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 60 tablets (100 mg) Bottles of 30 tablets (1000 mg)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided	Adequate
Storage conditions	Provided	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	(b) (4) Addmedica SAS [print code] SIKLOS is a trademark of Addmedica.	Adequate

Conclusion:
1. Firm only mentioned the drug product should be stored below (b) (4) Firm has been requested to change the storage conditions in PI, container and carton labels to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]."
2. (b) (4)
3. Firm has been requested to add "To decrease the risk of contact, advise caregivers to wear disposable gloves when handling Siklos or bottles containing Siklos" at the

beginning paragraph of 16.3. This is to be consistent with RLD DROXIA.
4. The name of manufacturer/distributor is not provided in PI.
5. Proposed NDC number should be submitted.

Above requests have been conveyed to the sponsor along with other disciplines' labeling review comments. Firm has made changes on items 1, 2, 4 and states "The labeler code request has been submitted to (b) (4) on 29 November 2016 and additional information provided NDC numbers are pending and will be added once received"

Firm did not make changes per item #3 above. Firm has provided the following justifications on 12-Dec-2016:

(b) (4)

Evaluation: Pharm/Tox reviewer Matthew Thompson replied in email on 19-Dec-2016 that "…… The National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings (2016) indicates hydroxyurea is an antineoplastic agent with a special warning on handling bottles and capsules. A NIOSH document (http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf#page=37) discusses exposure to antineoplastic drugs. "Some drugs defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (for example, coated tablets or capsules—solid, intact medications that are administered to patients without modifying the formulation). However, they may pose a risk if solid drug formulations are altered, such as by crushing tablets...". A condition for exposure is "Crushing tablets to make oral liquid doses". From a pharmacology/toxicology perspective, we recommend that individuals handling tablets wear disposable gloves as a form of personal protective equipment (PPE) and throw them out immediately after handling tablets to avoid contamination of surrounding surfaces with hydroxyurea. Individuals not taking the product could be exposed to hydroxyurea by touching surfaces that have been contaminated with hydroxyurea. The film-coating on the tablet may reduce the risk of exposure. If scored, film-coated tablets are broken into pieces, then individuals handling tablets should assume the film-coating is no longer effective and will not prevent exposure. To decrease the risk of contact, wear disposable gloves."

Per Pharm/Tox recommendation, firm will be required to add "To decrease the risk of

contact, advise caregivers to wear disposable gloves when handling Siklos or bottles containing Siklos" at the beginning paragraph of 16.3 of PI. Firm also needs to update medication guide and instruction for use. These will be conveyed to the sponsor.

The following IR was sent to the sponsor by Dr. Anamitro Banerjee on 17-Nov-2016:

(b) (4)

Firm's response on 28-Nov-2016:

(b) (4)

Evaluation: After discussion with Dr. Anamitro Banerjee, we think firm's response is acceptable.

R Regional Information

1.14 Labeling

Immediate Container Label (12/12/2016)

(b) (4)

Reviewer's Assessment: Adequate

Storage condition should be changed to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]"

Also refer to DMEPA's review for other changes/edits. The comment has been conveyed to the sponsor. The sponsor has made changes.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	Adequate; Refer to DMEPA review for other comments
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	No need to provide	Adequate
Net contents* (21 CFR 201.51(a))	60 tablets (100 mg) 30 tablets (1000 mg)	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for an oral dosage form	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
"Rx only" statement per 21 CFR	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate

Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Others		Adequate

Reviewer's Assessment: Adequate
Storage conditions should be changed to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]" The comment has been conveyed to the sponsor and firm has made changes.
Also refer to DMEPA's review for other comments.

Carton Labeling (12/12/2016)

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: Adequate

Storage conditions should be changed to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]" The comment has been conveyed to the sponsor and the firm has made changes. Refer to DMEPA's review for other comments.

List of Deficiencies: None (All comments have been conveyed to the sponsor.)

Primary Labeling Reviewer Name and Date: Xing Wang, Ph.D., 22-Dec-2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D., ONDPI/NDPBII Acting Branch Chief

Anamitro Banerjee

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Xing Wang

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CHAPTER VII: BIOPHARMACEUTICS

NDA: 208843-ORIG-1

Drug Product Name / Strength: Siklos® (hydroxyurea) 100 mg and 1000 mg tablets

Route of Administration: Oral

Applicant Name: Addmedica SAS

REVIEW SUMMARY

Background:

The Applicant submitted **NDA 208843** on 07/29/2016. The proposed drug product, **Siklos® (hydroxyurea) 100 and 1000 mg tablets**, is an antineoplastic agent, indicated 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.

Submissions:

07/29/2016	NDA 208843/Original submission
09/27/2016	eCTD-0004/Applicant's Response to Biopharmaceutics Information Requests
10/31/2016	eCTD-0008/Applicant's Response to Biopharmaceutics Information Requests
11/17/2016	eCTD-0011/Applicant's Response to Biopharmaceutics Information Requests
11/22/2016	eCTD-0012/Applicant's Response to Biopharmaceutics Information Requests
12/20/2016	eCTD-0015/Applicant's Response to Biopharmaceutics Information Requests

Review:

The focus of the Biopharmaceutics review was to evaluate the submitted information/ data and provide a recommendation on the acceptability of the following: 1) In Vitro Dissolution Test (method and acceptance criterion), 2) In Vitro Disintegration Test, 3) Bridging of formulations, 4) (b) (4)

(1) In Vitro Dissolution Test

Dissolution Method: The proposed in vitro dissolution method (USP Apparatus II, paddle, (b) (4) rpm, water, 500 mL for 100 mg tablets, and 1000 mL for 1000 mg tablets) seems adequate, pending the Applicant's justification for the use of (b) (4) 50 rpm.

Dissolution Acceptance Criterion: The original proposed dissolution acceptance criterion of *Q*= (b) (4) *minutes* was deemed permissive and was not accepted. Therefore, this Reviewer recommended a (b) (4) dissolution acceptance criterion of ***Q*** (b) (4) ***% in 15 minutes***, which was

accepted by the Applicant for batch release and stability testing; however, the acceptance criterion will be finalized after the Applicant responds adequately to the CR comment on the paddle speed.

(2) In Vitro Disintegration Test

Method: The disintegration test for the proposed drug product was performed according to the current USP <701> method. Overall, the proposed disintegration method was assessed and found acceptable.

Acceptance Criteria: The original proposed acceptance criteria for the disintegration test (b) (4) The recommended disintegration acceptance criterion was accepted by the Applicant for drug product batch release and stability testing.

(3) Bridging of Formulations

No change of the composition of the formulations occurred between the clinical studies (OTL001-01 clinical study and ESCORT-HU study) and the final composition of the proposed drug product; therefore, bridging studies were not needed.

(b) (4)

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(b) (4)

OVERALL COMMENTS AND RECOMMENDATIONS

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) paddle speed.

The proposed disintegration method and the revised acceptance criterion for the proposed drug product have been assessed and found acceptable.

(b) (4)

From the Biopharmaceutics perspective, NDA 208843, for Siklos® 1000 mg and 100 mg tablets, is recommended for a COMPLETE RESPONSE (CR).

Primary Biopharmaceutics Reviewer Name and Date:

Mei Ou, Ph.D. 01/18/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics Branch I (DBI)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Secondary Reviewer Name and Date:

Okpo Eradiri, Ph.D. 01/23/2017
Activing Biopharmaceutics Lead
Division of Biopharmaceutics Branch I (DBI)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Tertiary Reviewer Name and Date:

Angelica Dorantes, Ph.D. 01/27/2017
Activing Branch Chief
Division of Biopharmaceutics Branch I (DBI)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Angelica Dorantes

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Okponanabofa Eradiri

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Functionally Scored Tablets: Content uniformity (based on uneven split)	• Formulation changes on the approved scored tablets • Process parameters • Scale/equipments • Site	L		Acceptable	
Functionally Scored Tablets: Friability	• Formulation and/ on the approved scored tablets • Process parameters • Scale/equipments • Site	L	Firm has provided breakability data of a batch (# 60809) of engraved Siklos 1000 mg film-coated tablets manufactured by (b) (4) The result is acceptable	Acceptable	On 13-Oct-2016, Addmedica commits that the data for the assessment of breakability close to the shelf-life will be provided to the FDA in the annual report or upon FDA request.

(b) (4)

Anamitro Banerjee

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