CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 208843
Supporting document/s:	19
Applicant's letter date:	June 30, 2017
CDER stamp date:	June 30, 2017
Product:	Hydroxyurea (SIKLOS, 100 and 1000 mg tablets)
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
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Matthew D Thompson, PhD, MPH
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD Ann Farrell, MD (DHP)
Project Manager:	Rachel McMullen, MPH

Disclaimer

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1 Executive Summary

1.1 Introduction

Hydroxyurea is an antimetabolite used to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises. Evidence indicates hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. In patients with sickle cell anemia, known pharmacologic effects of hydroxyurea that may contribute to its beneficial effects include increasing hemoglobin F levels in red blood cells (RBCs), decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium. Hydroxyurea was initially approved by the FDA in 1967.

The Applicant, Addmedica SAS, has resubmitted this 505(b)(2) NDA to support the use of hydroxyurea (SIKLOS, 100 and 1000 mg 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 with recurrent moderate to severe painful crises. DROXIA (Bristol Myers Squibb) is the listed drug for this application. DROXIA (hydroxyurea capsules, USP) is available for oral use as capsules containing 200 mg, 300 mg, and 400 mg hydroxyurea. The recommended dosing for SIKLOS is consistent with the DROXIA label. The resubmission contains no new nonclinical data for review.

1.2 Brief Discussion of Nonclinical Findings

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).

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, hydroxyurea (SIKLOS) may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

At the time of this review, the labeling negotiations with the Applicant are ongoing. The nonclinical sections of the label will be comparable to the label of DROXIA, the listed drug. The Applicant has proposed two notable changes from the DROXIA label.

1) In Section 8.3 on male contraception, the Applicant is proposing males use contraception (b) (4). The DROXIA label indicates male contraception for at least 1 year after therapy. (b) (4)

Pharmacology/Toxicology has no issues with the Applicant's proposal (b) (4). The Clinical team's input has been sought to determine acceptability of this labeling change.

2) The Applicant (b) (4) hydroxyurea tablets.

SIKLOS is considered an antimetabolite and antineoplastic drug, and individuals handling tablets should take the same precautions as if handling HYDREA. Relevant parts of section 16.3 of the HYDREA label for handling and storage include:

> "…Follow applicable special handling and disposal procedures [see References (15)].
>
> To decrease the risk of contact, advise caregivers to wear disposable gloves when handling HYDREA or bottles containing HYDREA… Avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs on the skin, wash affected area immediately and thoroughly with soap and water…"

Reference 15 refers the reader to the Occupational Safety and Health Administration's website for hazardous drugs. The website contains a number of recommendations for the safe handling of antineoplastic drugs, including wearing gloves.

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 the Pharmacology/Toxicology perspective, we recommend that individuals handling tablets wear disposable gloves as a form of personal protective equipment

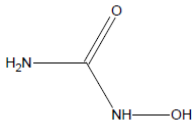
(PPE) and throw them out immediately after handling tablets to avoid contamination of surrounding surfaces with hydroxyurea. Individuals not taking the product could be exposed to hydroxyurea by touching surfaces that have been contaminated with hydroxyurea.

Though the film-coating on the tablets may reduce the risk of exposure, if scored and broken, individuals handling the tablets should assume the film-coating is no longer effective and will not prevent exposure. Therefore, to decrease the risk of contact with hydroxyurea, individuals should wear disposable gloves.

2 Drug Information

2.1 Drug

CAS Registry Number
127-07-1
Generic Name
Hydroxyurea
Chemical Name
N-Hydroxyurea; Hydroxycarbamine
Molecular Formula
$CH_4N_2O_2$
Molecular Weight
76.05 g/mol
Structure or Biochemical Description



Pharmacologic Class
Antimetabolite

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 124352 (SIKLOS, Addmedica SAS); NDA 016295 (DROXIA, Bristol Myers Squibb); NDA 016295 (HYDREA, Bristol Myers Squibb); DMF (b) (4)

2.3 Drug Formulation

DROXIA (hydroxyurea capsules, USP), the listed drug, is available for oral use as capsules containing 200 mg, 300 mg, and 400 mg hydroxyurea. DROXIA inactive ingredients include citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide, and capsule colorants. SIKLOS tablets will be film-coated.

Table 1: Formulation of SIKLOS Tablets

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)

(Excerpted from Applicant's Submission)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The Applicant identified a new degradation product, (b) (4), in the hydroxyurea (SIKLOS) tablets.

(b) (4)

We note that the Applicant is relying on nonclinical studies in the scientific literature. A paper published (b) (4) as does hydroxyurea per the label. Beyond this paper, there is no nonclinical information for this impurity. The Applicant has proposed a mechanism for how the degradation product is formed.

Figure 1: Hypothetical Mechanism for the Formation of (b) (4)

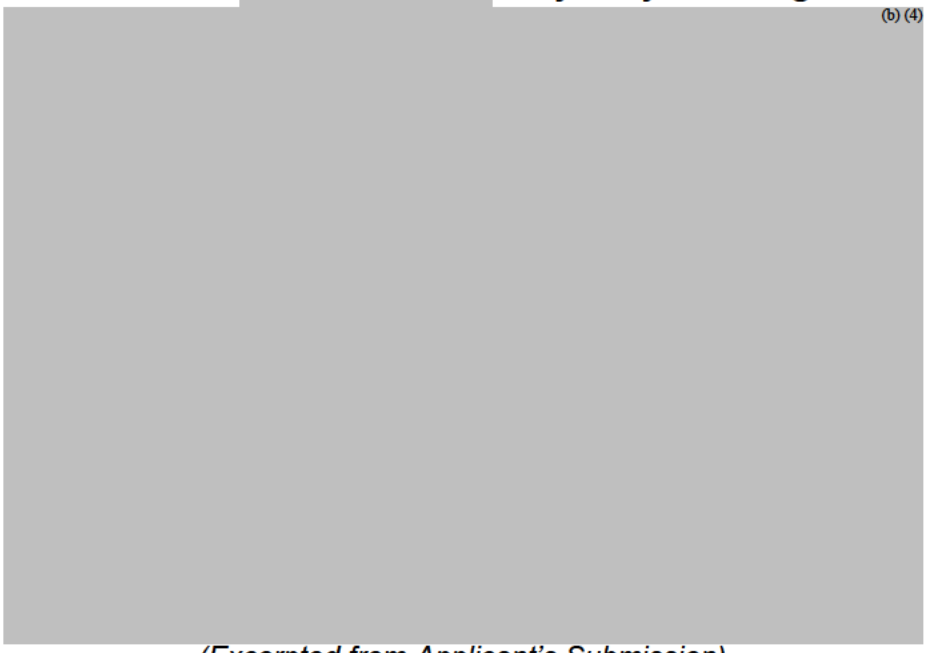
(b) (4)

(Excerpted from Applicant's Submission)

The Applicant submitted product quality data measuring levels of (b) (4) in SIKLOS, HYDREA, and DROXIA products.

Table 2: Levels of (b) (4) **in Hydroxyurea Drug Products**

(b) (4)



(Excerpted from Applicant's Submission)

The Applicant measured (b) (4) in their 100 mg and 1000 mg tablets at (b) (4) %, which is above the Q3B qualification threshold of 0.2%. The Applicant has also provided data showing that (b) (4) is present in European (HYDREA) and US (DROXIA) products, up to (b) (4) %, respectively. Given the DMF holder (b) (4) is referenced by both Addmedica (for SIKLOS, NDA 208843) and Bristol Myers Squibb

(for DROXIA, NDA 016295), Pharmacology/Toxicology accepts the side by side comparison of SIKLOS with DROXIA regarding the presence (b) (4)

Since the Applicant has shown that FDA-approved DROXIA has some amount of the (b) (4) (b) (4) impurity, Pharmacology/Toxicology views DROXIA as setting a precedent for (b) (4) given the clinical experience with DROXIA and its established safety profile. Based on historical use of hydroxyurea, and the presence of this impurity in approved products, Pharmacology/Toxicology has no outstanding concerns with this impurity. The Applicant originally set the (b) (4) specification at (b) (4) % but proposed lowering it to NMT (b) (4) % in response to an FDA information request.

2.6 Proposed Clinical Population and Dosing Regimen

Addmedica SAS proposed dosing recommendations that are consistent with current DROXIA labeling for the treatment of sickle cell anemia. The recommended initial dose of SIKLOS is 20 mg/kg/day compared to 15 mg/kg/day for DROXIA. Both have recommended dose increases of 5 mg/kg/day (SIKLOS every 8 weeks and DROXIA every 12 weeks). Both have a maximum recommended dose of 35 mg/kg/day.

2.7 Regulatory Background

Orphan-drug designation was granted on July 24, 2013. A pre-NDA meeting occurred on December 11, 2014 to discuss the data package to support market registration. A question on the nonclinical package was discussed. A Type C meeting occurred on October 22, 2015 to discuss CMC and clinical data for the NDA submission. No nonclinical issues were discussed. A Type C meeting occurred on June 14, 2016. No nonclinical issues were discussed.

Addmedica SAS submitted the original 505(b)(2) NDA on July 29, 2016. Due to deficiencies (b) (4) a Complete Response letter was issued on February 9, 2017. The resubmission (June 30, 2017) sought to address deficiencies raised in the CR letter.

3 Studies Submitted

None

4 Pharmacology

No new pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

Not submitted

6 General Toxicology

Not submitted

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

Not submitted

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW D THOMPSON
10/17/2017

CHRISTOPHER M SHETH
10/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Supporting document/s:	1
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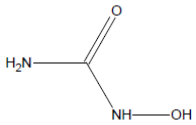
2 Drug Information

2.1 Drug

CAS Registry Number
127-07-1
Generic Name
Hydroxyurea
Chemical Name
N-Hydroxyurea; Hydroxycarbamine
Molecular Formula
$CH_4N_2O_2$
Molecular Weight
76.05 g/mol
Structure or Biochemical Description



Pharmacologic Class
Antimetabolite

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(Excerpted from Applicant's Submission)

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Not submitted

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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/s/

MATTHEW D THOMPSON
01/09/2017

CHRISTOPHER M SHETH
01/09/2017