CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	7 December 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208843
Product Name and Strength:	Siklos (hydroxyurea) 100 mg and 1,000 mg tablet
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Addmedica SAS
Submission Date:	7 December 2017
OSE RCM #:	2017-1375-1
DMEPA Primary Reviewer:	Rhiannon Leutner, PharmD, MPH, MBA
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Siklos (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Siklos are acceptable from a medication error perspective. We have no further recommendations at this time.

[a]Leutner R. Label and Labeling Review for Siklos (NDA 208843). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 16. RCM No.: 2017-1375.

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/s/

RHIANNON LEUTNER
12/07/2017

HINA S MEHTA
12/08/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	21 November 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208843
Product Name and Strength:	Siklos (hydroxyurea) 100 mg and 1,000 mg tablet
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Addmedica SAS
Submission Date:	29 July 2016 and 21 October 2016
OSE RCM #:	2016-1805
DMEPA Primary Reviewer:	Rhiannon Leutner, PharmD, MPH, MBA
DMEPA Team Leader (Acting):	Hina Mehta, PharmD
DMEPA Deputy Director:	Lubna Merchant, M.S., PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the Prescribing Information, Medication Guide, Instructions for Use, and carton and container labels submitted for Siklos (NDA 208843) to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Addmedica submitted NDA 208443 to obtain marketing approval of Siklos (hydroxyurea) tablets. Siklos is intended for treatment 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 crises. Siklos will be available as 100 mg and 1,000 mg tablets and the initial recommended dosing is 20 mg/kg with increases of 5 mg/kg/day every 8 weeks up to a maximum of 35 mg/kg/day.

DMEPA performed a risk assessment of the proposed Siklos Prescribing Information, Medication Guide, Instructions for Use (IFU), the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

Prescribing Information, Medication Guide, IFU

We provide recommendations for improvement to the Dosage and Administration, Dosage Forms and Strength, and the How Supplied Sections of the proposed PI and have proposed them in tracked changes in Appendix F.

There are a number of potential calculated doses that will fall between the available doses (1,000 mg, 750 mg, 500 mg, 250 mg, 100 mg, and combinations thereof). We suggest requesting the Sponsor provide a table with recommended rounding parameters based on weight in the prescribing information to reduce the potential for dosing errors.

The prescribing information notes that the split tablets can be mixed with (b) (4) We recommend the prescribing information clarify what type of (b) (4) is intended as we do not believe this is a common household product. Additionally, it is noted that the tablets may also be mixed (b) (4)

The product labeling should be revised to use commas every three decimal places in numbers containing four or more digits. (e.g. 1,000 mg). We note the use of symbols, absence of commas, and offer comments to improve clarity of the prescribing information as well as highlight points in need of consistency. For example, the highlights describe the 1,000 mg tablet as "(b) (4)" tablet and Section 2 describes a "tablet with triple scoring on both sides which can be divided in four equal parts" – similar edits are provided for the proposed Instructions for Use and Medication Guide. Several areas are in need of improvement to ensure consistency between sources of information.

Siklos is a cytotoxic drug that can cause harm. We note that best practices for institutional settings call for solid oral preparations (tablets) of cytotoxic drugs to be cut within the biological safety cabinet.[a] It is unclear how the Sponsor has proposed to mitigate this risk for the home setting. The prescribing information, IFU and Medication Guide do not specify the use of personal protective equipment (PPE). When the tablet is broken (as is required when breaking the 1,000 mg tablet for smaller doses), patients and caregivers must avoid touching the broken surface. It is difficult to ascertain the feasibility of this directive without product samples. We have requested samples of this scored tablet and the Sponsor is unable to provide those tablets at this time. We may suggest further consideration of this risk of touching a broken surface, upon receiving samples from the Sponsor. We note the Guidance for Industry Tablet Scoring:

[a] Easty AC, Coakley N, Cheng R, et al. Safe handling of cytotoxics: guideline recommendations. Current Oncology. 2015;22(1):e27-e37. doi:10.3747/co.21.2151. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4324350/

Nomenclature, Labeling, and Data for Evaluation states that "the split tablet should be safe to handle and not pose risk of unintended drug exposure."[b] It's unclear if this tablet would be considered "safe to handle" once broken if it had a small surface area safe for handling.

We revised the IFU to clarify what to do if accidental contact with skin occurs, which was previously located in the prescribing information and Medication Guide but not in the IFU, which is what a patient or caregiver will most likely be using at the time that this accidental exposure would occur. Additional guidance was added for individuals who may wear contacts and experience accidental exposure to the eye(s). The IFU visuals depicting a spoon, a spoon brought to an adult's mouth, and an adult administering medication via a teaspoon to a child do not offer useful information and are potentially confusing. Comments were provided to address this area of improvement in Appendix F. General formatting and edits are also provided to improve the readability of the IFU. We provide recommendations in Section 4.1 in order to promote the safe use of this product.

Carton and Container Labels

The proposed Siklos container label contains an established name which lacks prominence commensurate with the proprietary name. The proprietary name as proposed includes "1,000 mg" and "100 mg" statements adjacent to the name do not provide adequate white space for optimal readability. Additionally, the proposed tablet graphic is more prominent than other critical information. The principal display panel (PDP) of the container labels should be revised to ensure the following critical information is most prominent: proprietary name, established name, product strength, route of administration, warnings or cautionary statements. The placement and size of the net quantity statement on the carton and container labels may confuse end users and potentiate the risk for wrong dose errors. The proposed carton and container labels show the net quantity (30 and 60 tablets) more prominently than the product strength (1,000 mg and 100 mg). Therefore, it should be relocated away from the product strength, such as to the bottom of the PDP.

The PDP labeling should note that a Medication Guide should be dispensed to each patient, in accordance with 21 CFR 208.24(d). The manufacturer information can be moved to the side panel – as proposed, it clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength. We recommend revisions to the Usual Dose statement in accordance with 21 CFR 201.55.

As currently presented, the NDC number is located at the bottom of the container labeling and on the inside closure flap of carton labeling. Since NDC number is often used as an additional

[b] Guidance for Industry. Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. March 2013. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269921.pdf

verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i). Additionally, we request the Sponsor provide the proposed NDC in lieu of the currently depicted placeholder (XXXXX-XXXX-XX).

The expiration date and lot number statements are in need of improvement. It is unclear what is intended by "Lot:/ Partij: / Ch.-B.:" and "EXP: / EXP: / Verw. bis:" and we recommend extraneous information be removed. The carton labeling should be revised to include lot numbers. The Unites States Distributor address may also be added to the container label and carton labeling to provide readily available US contact information for this product.

The order and prominence of product information on the carton and container labeling can be revised for improved readability and clarity. We provide recommendations in Section 4.2 in order to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Siklos labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Based on this review, we recommend revisions to the proposed PI in tracked changes for review and consideration by DHP. See Appendix F for tracked change edits in the proposed PI.
2. Consider requesting the Sponsor provide recommended rounding parameters necessary for weight-based dosing in the prescribing information. Additional instructions on how to round calculated doses may help ensure that the appropriate number of the tablets of the appropriate strength will be prescribed/dispensed. For example, if a dose is calculated at 225 mg, additional information is needed to determine if it is appropriate to round up to 250mg for a quarter tab of the 1,000 mg tablet or if it should be rounded down to 200 mg and the dose should be prescribed/dispensed as two 100 mg tablets.
3. Consider a modification to the heading in Table 1: Dosing Recommendation Based on Blood Counts – "Dosing Adjustment Based on Blood Counts." Adding the word "adjustment" will help specify this is an adjustment that follows initiation rather than a different option for initiation.
4. Revise prescribing information to use a comma in all reference to a 1,000 mg tablet. Further, use commas every three decimal places in numbers of four or more digits (e.g. "2,000 cells/mm3")

5. Consider replacing the symbols "<" and "≥" with their intended meanings ("less than") to prevent misinterpretation and confusion.[c]
6. Consider clarifying what type of (b) (4) may be mixed with the split tablets. It is unclear if this " (b) (4) would be a common household product. Consider clarifying what types (b) (4) would be acceptable mixing agents for split tablets. Consider naming acceptable (b) (4)
7. Ensure consistency with the nomenclature used for the scored tablet. The highlights describe a " (b) (4)" tablet while Section 3 describes a "triple scored" tablet.
8. Placeholders (XXXXX-XXXX-XX) are present for NDC numbers. Request the Sponsor submit proposed NDC numbers to the Agency for review.
9. Consider the need for the use of personal protective equipment (PPE) in Section 16.3.
10. Consider adding additional information to Section 16.3 concerning accidental exposure to the eye(s) for those who wear contact lenses to clarify that contact lenses should be removed immediately before flushing.

B. Medication Guide

1. Based on this review, we recommend revisions to the proposed Medication Guide in tracked changes for review and consideration by DHP. See Appendix F for tracked change edits in the proposed Medication Guide.
2. Use commas every three decimal places in numbers of four or more digits.
3. Consider adding additional information concerning accidental exposure to the eye(s) for those who wear contact lenses to clarify that contact lenses should be removed immediately before flushing.

C. Instructions for Use (IFU)

1. Based on this review, we recommend revisions to the proposed IFU in tracked changes for review and consideration by DHP. See Appendix F for tracked change edits in the proposed IFU.
2. Section headings and revisions have been proposed and to clarify the instructions.
3. Use commas every three decimal places in numbers of four or more digits.
4. Considering the need for the use of personal protective equipment (PPE), revise IFU images to depict gloved hands during preparation.
5. Consider adding language to instruct a patient or caregiver on what to do if they touch the broken surface, right at the step of breaking the tablet, which is where they should be if/when this exposure were to occur.

[c] Draft Guidance: Container and Carton, April 2013 (lines 242-244, 479). http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

6. Consider clarifying what type of (b) (4) may be mixed with the split tablets. It is unclear if this "(b) (4) would be a common household product. Consider clarifying what types (b) (4)
7. The IFU visuals depicting a spoon, a spoon brought to an adult's mouth, and an adult administering medication via a teaspoon to a child do not offer useful information and are potentially confusing. In general, these visuals do not add clarity to the step of combining tablets in water or food. A close up visual that showed broken tablets on a spoon combined with an acceptable mixing agent would be of greater value.

4.2 RECOMMENDATIONS FOR ADDMEDICA SAS

We recommend the following be implemented prior to approval of this NDA:

A. Container and Carton Labels
   1. Revise product labeling to use commas every three decimal places in numbers containing four or more digits. (e.g. 1,000 mg)
   2. Revise the labels to ensure the proprietary and established names the most prominent information on the label.
   3. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

For example:

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Siklos [NDA 208843] that Addmedica SAS submitted on 21 October 2016.

Table 2. Relevant Product Information for Siklos	
Initial Approval Date	N/A
Active Ingredient	hydroxyurea
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 crises
Route of Administration	oral
Dosage Form	immediate release film-coated tablet
Strength	100 mg and 1,000 mg
Dose and Frequency	Initial recommended dosing is 20 mg/kg as a single dose with increases of 5 mg/kg/day every 8 weeks up to a maximum of 35 mg/kg/day
How Supplied	The 100 mg will be supplied in bottles of 60 tablets. The 1,000 mg will be supplied in bottles of 30 tablets
Storage	Store below 25°C (77°F). Keep tightly closed. Broken 1000 mg tablets must be stored in the bottle and must be used within three months
Container Closure	High-density polyethylene bottle with a child-resistant cap

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis[d], along with postmarket medication error data, we reviewed the following Siklos labels and labeling submitted by Admedica SAS.

1. Container label submitted on 29 July 2016
2. Carton labeling submitted on 29 July 2016
3. Prescribing Information submitted on 21 October 2016
4. Medication Guide submitted on 21 October 2016
5. Instructions for Use submitted on 21 October 2016

F.2 Label and Labeling Images

Container Labels

(b) (4)

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/s/

RHIANNON LEUTNER
11/21/2016

HINA S MEHTA
11/21/2016

LUBNA A MERCHANT
11/21/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 8, 2017
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SIKLOS (hydroxyurea)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208843
Applicant:	Voisin Consulting Life Sciences on behalf of Addmedica SAS

1 INTRODUCTION

On June 30, 2017, Voisin Consulting Life Sciences on behalf of Addmedica SAS submitted for the Agency's review a Class 2 Resubmission for 505(b)(2) New Drug Application (NDA) 208843 for SIKLOS (hydroxyurea) tablets. The purpose of this resubmission is to address the deficiencies identified in the Complete Response (CR) letter issued by the Agency on February 9, 2017.

The proposed indication is 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on July 19, 2017 and July 26, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SIKLOS (hydroxyurea) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on October 16, 2017.

2 MATERIAL REVIEWED

- Draft SIKLOS (hydroxyurea) MG and IFU received on June 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 3, 2017.
- Draft SIKLOS (hydroxyurea) Prescribing Information (PI) received on June 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 3, 2017.
- Approved DROXIA (hydroxyurea) comparator labeling dated March 23, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
11/08/2017

RACHAEL E CONKLIN
11/08/2017

MORGAN A WALKER
11/08/2017

BARBARA A FULLER
11/08/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/8/17

To: Rachel McMullen, Regulatory Project Manager, (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Lisa Hubbard, Deputy Director, OPDP

Subject: OPDP Labeling Comments for SIKLOS (hydroxyurea)

NDA: 208843

In response to DHP's consult request dated July 26, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for SIKLOS (hydroxyurea) tablets, for oral use.

PI and PPI/Medication Guide/IFU: OPDP previously provided comments on the proposed labeling on December 27, 2016. We refer to our previous consult response (attached) and we do not have any additional comments on the draft PI that was emailed to OPDP on November 3, 2017.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling accessed from the shared drive and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at (240) 402-8189 or rachael.conklin@fda.hhs.gov.

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/s/

RACHAEL E CONKLIN
11/08/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	16 October 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208843
Product Name and Strength:	Siklos (hydroxyurea) 100 mg and 1,000 mg tablet
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Addmedica SAS
Submission Date:	30 June 2017
OSE RCM #:	2017-1375
DMEPA Primary Reviewer:	Rhiannon Leutner, PharmD, MPH, MBA
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the Prescribing Information, Medication Guide, Instructions for Use, and carton labeling and container labels submitted for Siklos (NDA 208843) to determine if they are acceptable from a medication error perspective. The revisions to the container labels and carton labeling are in response to previous label and labeling review recommendations.[a,b]

1.1 REGULATORY HISTORY

NDA 208843 for Siklos (hydroxyurea) was previously submitted on 29 July 2016 and received a complete response on 9 February 2017. The resubmission for NDA 208843 was received on 30 June 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Addmedica submitted a response to a Complete Response for NDA 208443 to obtain marketing approval of Siklos (hydroxyurea) tablets. Siklos is intended for treatment 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 crises.

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[a] Leutner RM. Label and Labeling Review for Siklos (NDA 208843). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 21 Nov 16. OSE RCM No.: 2016-1805.

[b] Leutner RM. Label and Labeling Memo for Siklos (NDA 208843). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 9 Jan 17. OSE RCM No.: 2016-1805-1.

Siklos will be available as 100 mg and 1,000 mg tablets and the initial recommended dosing is 20 mg/kg with increases of 5 mg/kg/day every 8 weeks up to a maximum of 35 mg/kg/day. DMEPA performed a risk assessment of the proposed Siklos Prescribing Information, Medication Guide, Instructions for Use (IFU), the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

Our previous reviews provided recommendations for revision to the Prescribing Information, Medication Guide, Instructions for Use, and carton and container labels, some of which have been incorporated to the revised labeling for Siklos. However, Addmedica's proposed revisions are in need of improvement to address the deficiencies that may lead to medication errors.

Prescribing Information, Medication Guide, IFU

Dose Rounding

This product is available in 1,000 mg and 100 mg tablets. The 1,000 mg tablets have 3 score lines and can be split into 4 parts (each 250 mg). Therefore, the two strengths can be used to deliver doses of 1,000 mg, 750 mg, 500 mg, 250 mg, 100 mg, and combinations thereof. Calculated doses may fall outside of the available strengths (or combinations) and guidance is necessary to instruct prescribers when to round to the nearest 50 mg or 100 mg increments. For example, a weight-based dose may be calculated at 225 mg and doses available are 200 mg and 250 mg. The proposed dosing table (Table 2) in Section 2.1 *Dosing Information* of the Prescribing Information does not provide rounding guidance. Additionally, this table is difficult to read and may lead to dosing errors. We recommend removing this table and providing general a recommendation to instruct prescribers on how to round calculated doses. Specific language is provided for consideration in Section 4.

Need for tablet splitter

We received samples of the 1,000 mg tablet on 12 December 2016. We did not experience difficulty breaking the tablets by hand into two 500 mg parts but the 500 mg parts were difficult to break into two 250 mg parts by hand. Therefore, we recommend the use of a tablet splitter for breaking the 1,000 mg tablet. DMPP concurred with this recommendation.[c] We previously recommended that Addmedica consider adding a section to the beginning of the IFU to state what materials will be needed and we now suggest adding a tablet splitter to this list of materials needed. We note they did not incorporate such a revision and we defer to DMPP on the appropriateness of this consideration. Specific language concerning the need for tablet splitter is provided for consideration in Section 4.

NDC product code

The currently proposed NDC numbers, [redacted] (b) (4), in Section 16.1 *How Supplied* utilize sequential numbering for the product codes. This similarity of product code

[c] Email communication; 16 Dec 2016; Morgan Walker [Labeling Reviewer, OMPT/CDER/OMP/OMPI/DMPP]

numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., (b) (4)). We recommend the NDC numbers be revised to avoid the use of sequential numbering in product codes.

Carton Labeling and Container Labels

All references in carton labeling and container labels should include a comma every three decimal places in numbers containing four or more digits (e.g. 1,000 mg tablet). This comma should be added to the 1,000 mg container label.

We previously requested the PDP labeling should note that a Medication Guide should be dispensed to each patient, in accordance with 21 CFR 208.24(d). This information needs to be added to the 100 mg tablet container label.

The currently proposed NDC numbers, (b) (4) numbering for the product codes. This similarity of product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment (b) (4) is not an effective differentiating feature (e.g., (b) (4)). We recommend the NDC numbers be revised (b) (4)

As currently presented, the NDC number on the carton labeling is located in close proximity to the strength statement. We recommend moving the NDC on carton labeling to the top of the PDP above the product name. This revision will keep it prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i). It may be necessary to reduce the size of the graphic on the carton labeling to ensure readability of important product information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Siklos labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2.1 Dosing Information
    a. The proposed dosing table (Table 2) does not provide dose rounding guidance. Additionally, this table is difficult to read. As proposed, it may lead to dosing errors. We recommend removing this table and inserting the following general rounding recommendation:

        Siklos is available in 100 mg and 1,000 mg tablets. The 1,000 mg tablets have 3 score lines and can be split into 4 parts (each 250 mg). Therefore,

the two strengths can be used to deliver doses of 1,000 mg, 750 mg, 500 mg, 250 mg, 100 mg, and combinations thereof. Calculated doses should be rounded to the nearest 50 mg or 100 mg strength based on clinical judgment.

2. Section 16.1 How Supplied
    a. The currently proposed NDC numbers, [redacted] (b) (4) numbering for the product codes. This similarity of product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment [redacted] (b) (4) is not an effective differentiating feature (e.g., [redacted] (b) (4)). We recommend the NDC numbers be revised to avoid the use of [redacted] (b) (4) product codes. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increased their size in comparison to the remaining digits in the NDC number of put them in bold type. For example, XXXX-**XXX**-XX

B. Instructions for Use (IFU)

1. Include a Materials Needed Section at the beginning of the IFU.
2. Recommend adding a tablet splitter to the materials needed section.

4.2 RECOMMENDATIONS FOR ADDMEDICA SAS

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling

1. Revise product labeling to use commas every three decimal places in numbers containing four or more digits. (e.g. 1,000 mg). A comma should be added to the 1,000 mg container label.[d]
2. Revise the NDC numbers to avoid the use of [redacted] (b) (4) product codes. The currently proposed NDC numbers, [redacted] (b) (4) product codes. This similarity of product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment [redacted] (b) (4) is not an effective differentiating feature (e.g., [redacted] (b) (4)). If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increased their size in comparison to the remaining digits in the NDC number of put them in bold type. For example, XXXX-**XXX**-XX
3. As currently presented, the NDC number on the carton labeling is located in close proximity to the strength statement. We recommend moving the NDC on carton

[d] Draft Guidance: Container and Carton, April 2013 (lines 475-476).
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

labeling to the top of the PDP above the product name. This revision will keep it prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i). Consider reducing the graphic size on the carton labeling to ensure readability of important product information.

4. Revise the 100 mg container label to note that a Medication Guide should be dispensed to each patient, in accordance with 21 CFR 208.24(d).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Siklos [NDA 208843] that Addmedica SAS submitted on 30 June 2017.

Table 2. Relevant Product Information for Siklos	
Initial Approval Date	N/A
Active Ingredient	hydroxyurea
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 crises
Route of Administration	oral
Dosage Form	immediate release film-coated tablet
Strength	100 mg and 1,000 mg
Dose and Frequency	Initial recommended dosing is 20 mg/kg as a single dose with increases of 5 mg/kg/day every 8 weeks up to a maximum of 35 mg/kg/day
How Supplied	The 100 mg will be supplied in bottles of 60 tablets. The 1,000 mg will be supplied in bottles of 30 tablets
Storage	Store below 25°C (77°F). Keep tightly closed. Broken 1000 mg tablets must be stored in the bottle and must be used within three months.
Container Closure	High-density polyethylene bottle with a child-resistant cap

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis[e], along with postmarket medication error data, we reviewed the following Siklos labels and labeling submitted on 30 June 2017 by Admedica SAS.

- Prescribing Information
- Container labels
- Carton labeling

F.2 Label and Labeling Images

Container Labels

(b) (4)

[redacted]

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

RHIANNON LEUTNER
10/16/2017

HINA S MEHTA
10/18/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	9 January 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208843
Product Name and Strength:	Siklos (hydroxyurea) 100 mg and 1,000 mg tablet
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Addmedica SAS
Submission Date:	8 December 2016
OSE RCM #:	2016-1805-1
DMEPA Primary Reviewer:	Rhiannon Leutner, PharmD, MPH, MBA
DMEPA Team Leader (Acting):	Hina Mehta, PharmD
OMEPRM Deputy Director (Acting):	Lubna Merchant, M.S., PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised Prescribing Information, Medication Guide, Instructions for Use, and carton and container labels submitted for Siklos (NDA 208843) to determine if they are acceptable from a medication error perspective. The revisions to the container labels are in response to previous label and labeling review recommendations.[a]

2 DISCUSSION

Our previous review provided recommendations for revision to the Prescribing Information, Medication Guide, Instructions for Use, and carton and container labels, some of which have not been incorporated to the revised labeling for Siklos. Addmedica's proposed revisions are in need of improvement to address the deficiencies that may lead to medication errors.

Dose Rounding

This product is available in 1,000 mg and 100 mg tablets. The 1,000 mg tablets have 3 score lines and can be split into 4 parts (each 250 mg). Therefore, the two strengths can be used to deliver doses of 1,000 mg, 750 mg, 500 mg, 250 mg, 100 mg, and combinations thereof. Calculated doses may fall outside of the available strengths (or combinations) and guidance is necessary to instruct prescribers when to round to the nearest 50 mg or 100 mg increments. For example, a weight-based dose may be calculated at 225 mg and doses available are 200 mg and 250 mg. The proposed dosing table (Table 2) in *Section 2.1 Dosing Information* of the Prescribing Information does not provide rounding guidance. Additionally, this table is difficult to read and may lead to dosing errors. We recommend removing this table and providing general a recommendation to instruct prescribers on how to round calculated doses. Specific language is provided for consideration in Section 4.

Personal Protective Equipment (PPE)

We previously noted that precautions, such as wearing disposable gloves, should be taken when handling Siklos. The review team confirmed 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.[b] NIOSH states, "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 or making solutions from them outside a ventilated cabinet."[c] The revised labeling instructs patients and caregivers to avoid touching

[a] Leutner RM. Label and Labeling Review for Siklos (NDA 208843). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 21 Nov 16. OSE RCM No.: 2016-1805.

[b] Email communication; 19 Dec 2016; Matthew Thompson [Pharmacologist, OMPT/CDER/OND/OHOP/DHOT]

the broken surface of broken tablets. This is particularly difficult to do without the use of gloves, particularly when handling 250 mg doses due to the small surface area. Therefore, we recommend the Prescribing Information, Medication Guide, and Instructions for Use be revised to note the need for gloves when handling broken Siklos tablets. Previously, we noted the visual aids depicted in the IFU should include gloved hands and this was not incorporated into the revisions. We continue to recommend such a revision and defer to the Division of Medical Policy Programs (DMPP) on the appropriateness of this consideration. Specific language concerning the need for gloves is provided for consideration in Section 4 and Section 5.

Need for tablet splitter

We received samples of the 1,000 mg tablet on 12 December 2016. We did not experience difficulty breaking the tablets by hand into two 500 mg parts but the 500 mg parts were difficult to break into two 250 mg parts by hand. Therefore, we recommend the use of a tablet splitter for breaking the 1,000 mg tablet. DMPP concurred with this recommendation.[d] We previously recommended that Addmedica consider adding a section to the beginning of the IFU to state what materials will be needed and we now suggest adding a tablet splitter to this list of materials needed. We note they did not incorporate such a revision and we defer to DMPP on the appropriateness of this consideration. Specific language concerning the need for tablet splitter is provided for consideration in Section 4.

Carton and Container Labeling

We recommend a warning statement be added to the Siklos carton and container labeling to warn patients and caregivers that they need to wear disposable gloves when handling Siklos or bottles containing Siklos. If there is not sufficient space for this warning statement on the container label of the 100 mg tablet, we recommend it be added to the carton label.

We previously noted that placement and size of the net quantity statement on the carton and container labels may confuse users and potentiate the risk for wrong dose errors. The proposed carton and container labels show the net quantity (30 and 60 tablets) more prominently than the product strength (1,000 mg and 100 mg). For the 100 mg tablet, the net quantity of 60 tablets is more prominently displayed than the strength statement, 100 mg per tablet. We recommend the "60" is unbolded and the location of these two statements are replaced with one another. For the 1,000 mg tablet, the net quantity of 30 tablets is prominently displayed at the top of the side panel in bold. We recommend removing bold font, and moving to the bottom of the principal display panel. Relocate the distributor statement to the side panel and place the net quantity at the bottom of this panel without bold text (see image in Section 4.2, also previously provided to Addmedica).

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[c] NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Publication Number 2004–165. September 2004. http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf#page=37

[d] Email communication; 16 Dec 2016; Morgan Walker [Labeling Reviewer, OMPT/CDER/OMP/OMPI/DMPP]

We note that labeling to state that a Medication Guide should be dispensed to each patient, in accordance with 21 CFR 208.24(d) was added to both carton labels and to the side panel of the container label of the 1,000 mg tablet. This statement was not added to the 100 mg tablet and we assume this is due to the small size of the 100 mg container label. We recommend this statement be moved to the principal display panel on the 1,000 mg container label. The temperature storage statement may be moved to the side panel and this will free up space for the Medication Guide statement to be placed prominently on the PDP. There is also blank white space on the principle display panel of both container labels that may be used to convey important information.

We previously requested the proposed NDC in lieu of the placeholder (XXXXX-XXXX-XX) currently depicted on the carton and container labeling and have not yet received this information. We also continue to recommend adding the Unites States Distributor address to the container label and carton labeling to provide readily available US contact information.

3 CONCLUSION

The revised the revised Prescribing Information, Medication Guide, Instructions for Use, and carton and container labels container labels for Siklos (NDA 208843) are in need of improvement to address the deficiencies that may lead to medication errors.

4 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. *Section 2.1 Dosing Information*

a. The proposed dosing table (Table 2) does not provide dose rounding guidance. Additionally, this table is difficult to read. As proposed, it may lead to dosing errors. We recommend removing this table and inserting the following general rounding recommendation.

- Siklos is available in 100 mg and 1,000 mg tablets. The 1,000 mg tablets have 3 score lines and can be split into 4 parts (each 250 mg). Therefore, the two strengths can be used to deliver doses of 1,000 mg, 750 mg, 500 mg, 250 mg, 100 mg, and combinations thereof. Calculated doses should be rounded to the nearest 50 mg or 100 mg strength based on clinical judgment.

2. *Section 16.3 Handling and Disposal*

a. Consider inserting the following for consistency with DROXIA

- To decrease the risk of contact, advise caregivers to wear disposable gloves when handling Siklos.

B. Medication Guide

1. Consider inserting the following for consistency with DROXIA

a. Wear disposable gloves when handling Siklos or bottles containing Siklos.

C. Instructions for Use (IFU)

1. Include a Materials Needed Section at beginning of the IFU.
2. Recommend adding a tablet splitter to the materials needed section.
3. Revise IFU images to depict gloved hands during preparation.
4. (b) (4)
5.

5 RECOMMENDATIONS FOR ADDMEDICA SAS

We recommend the following be implemented prior to approval of this NDA:

A. Container Label
    1. Disposable glove warning
        i. We recommend a warning statement be added to the Siklos container labeling to warn patients and caregivers that they need to wear disposable gloves when handling Siklos or bottles containing Siklos.
    2. Revise net quantity statements
        i. We previously noted placement and size of the net quantity statement on the container labels may confuse end users and potentiate the risk for wrong dose errors. The revised carton labels show the net quantity (30 and 60 tablets) more prominently than the product strength (1,000 mg and 100 mg).
        ii. For the 1,000 mg tablet, the net quantity of 30 tablets is prominently displayed at the top of the side panel in bold. We recommend removing bold font, and moving to the bottom of the principal display panel. (see example below)

For example:

iii. For the 100 mg tablet, the net quantity of 60 tablets is more prominently displayed than the strength statement, 100 mg per tablet. We recommend removing bold from "60" and relocating the net quantity to be less prominent than the "100 mg per tablet" statement and relocating the "100 mg per tablet" to the principle display panel.

iv. For the 1,000 mg tablet, relocate the distributor statement to the side panel. This will provide sufficient space for the net quantity at the bottom of the principle display panel.

v. For the 1,000 mg tablet, relocate the temperature storage statement to the side panel. This will provide sufficient space for the medication guide statement on the principle display panel.

vi. Move the Medication Guide Statement from the side panel to the principal display panel on the 1,000 mg container label.

vii. There is a blank white space on the principle display panel of both container labels that should be used to convey important information.

3. Please provide the proposed NDC in lieu of the placeholder (XXXXX-XXXX-XX) currently depicted on the carton and container labeling.
4. Consider adding the Unites States Distributor address to the container label to provide readily available US contact information for this product.

B. Carton Label

1. Disposable glove warning
    i. We recommend a warning statement be added to the Siklos catron labeling to warn patients and caregivers that they need to wear disposable gloves when handling Siklos or bottles containing Siklos.

2. Please provide the proposed NDC in lieu of the placeholder (XXXXX-XXXX-XX) currently depicted on the carton and container labeling.
3. Consider adding the Unites States Distributor address to carton labeling to provide readily available US contact information for this product.

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/s/

RHIANNON LEUTNER
01/09/2017

HINA S MEHTA
01/10/2017

LUBNA A MERCHANT
01/10/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 27, 2016
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SIKLOS (hydroxyurea)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208843
Applicant:	Addmedica SAS

1 INTRODUCTION

On July 29, 2016, Addmedica SAS submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208843 for SIKLOS (hydroxyurea) tablets. This 505(b)(2) application relies on the FDA's previous finding of safety and effectiveness of DROXIA (hydroxyurea capsules, USP) NDA 016295 held by Bristol Myers Squibb. The proposed indication for SIKLOS (hydroxyurea) tablets 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 28, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SIKLOS (hydroxyurea) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft SIKLOS (hydroxyurea) tablets MG and IFU received on July 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 12, 2016.
- Draft SIKLOS (hydroxyurea) tablets Prescribing Information (PI) received on July 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 12, 2016.
- Approved DROXIA (hydroxyurea) comparator labeling dated July 16, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
12/27/2016

RACHAEL E CONKLIN
12/27/2016

BARBARA A FULLER
12/27/2016

LASHAWN M GRIFFITHS
12/27/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/27/16

To: Rachel McMullen, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Comments on draft labeling (Package Insert, Carton & Container Labeling) for Siklos (hydroxyurea) tablets, for oral use
NDA 208843

In response to your labeling consult request dated September 28, 2016 we have reviewed the draft Package Insert and draft carton and container labeling for SIKLOS (hydroxyurea) tablets, for oral use. This review is based upon the version of the draft PI accessed from the shared drive on December 22, 2016.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	"Most common adverse reactions to SIKLOS are: Incidence > 10%: (b) (4) includ (b) (4) neutropenia, (b) (4)	We note that the majority of these terms are not included in section 6.1. Was there any clinical trial experience for the ARs (b) (4) . (b) (4) (b) (4)

		(b) (4) [redacted]
2.1 Dosing Information	Table 2: Recommended SIKLOS dose rounding based on patient weight	This is a large table with numerous rows and columns, making it difficult to read. Would it be possible to apply shading to every other row?—This may improve the reader's ability to track across the rows (see attached PI on which I made this suggested change to the first few rows of the table).
2 Dosage and Administration: 2.1 Dosing Information	(b) (4) [redacted]	
2.1 Dosing Information	"The tablet should be taken once daily, (b) (4) [redacted] **with a glass of water** . . . ." (emphasis added)	(b) (4) [redacted]
2.1 Dosing Information	(b) (4) [redacted]	
2.1 Dosing Information		

	(b) (4)	
5.1 Myelosuppression	(b) (4)	
5.1 Myelosuppression		
5.3 Embryo-Fetal Toxicity		
5.4 Vasculitic Toxicities (including Leg Ulcers)		
5.5 Risks with Concomitant Use of Antiretroviral Drugs		
7 Drug Interactions	"*Peripheral Neuropathy* Peripheral neuropathy, which was severe in some cases, has been reported in patients with HIV infection receiving	Would it be possible to include a recommendation for action for providers (e.g., avoidance, monitoring, etc.)? With regard to promotion, we often look for the recommendations for action/management in a given situation to be included with risk information.

	hydroxyurea in combination with antiretroviral drugs, including didanosine, with or without stavudine."	
7.3 Concomitant Use of live Virus Vaccine	(b) (4)	
8.3 Females and Males of Reproductive Potential		
17 PATIENT COUNSELING INFORMATION		
17 PATIENT COUNSELING INFORMATION	"Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary	OPDP recommends that that each bullet/header relate to one counseling topic. We also note that some of the references to the sections of the labeling are not consistent with the current label and recommend

	malignancies including leukemia. Advise use of sun protection *[see Warnings and Precautions (5.1)]*."	revising. OPDP also recommends expanding on the information related to these two warnings and precautions to better reflect sections 5.2 and 5.4 and to be consistent with the Med Guide. E.g.: <u>Malignancies</u> Advise patients of the risk of malignancies including secondary leukemia and skin cancer. Advise patients to use sun protection and to monitor for the development of secondary malignancies *[see Warnings and Precautions (5.2)]*. <u>Vasculitic Toxicities</u> Advise patients of the risk of cutaneous vasculitic toxicities, including leg ulcers. Advise patients to report any signs or symptoms of vasculitic toxicities. Advise patients to report any leg wounds or ulcers prior to beginning treatment *[see Warnings and Precautions (5.4)]*.
17 PATIENT COUNSELING INFORMATION	Advise females and males of reproductive potential to use contraception during and after treatment with SIKLOS	OPDP recommends including the timeframes for use of contraception after treatment with SIKLOS.
17 PATIENT COUNSELING INFORMATION		OPDP recommends that information from section 5.6 be included here due to the risks associated with live virus vaccination.
17 PATIENT COUNSELING INFORMATION		OPDP recommends including information from section 16.3 regarding the handling of SIKLOS to this section as there are specific recommendations (with safety implications) for handling this product.

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/s/

RACHAEL E CONKLIN
12/27/2016