CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	October 22, 2015; 1:00 PM-2:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 124352
Product Name:	Siklos® (hydroxycarbamide).
Indication:	Treatment of Sickle Cell Anemia in Children
Sponsor/Applicant Name:	Addmedica SAS
Meeting Chair:	Nicole Gormley, MD, Acting Clinical Team Leader
Meeting Recorder:	Rachel McMullen, MPH, MHA, Regulatory Project Manager

FDA ATTENDEES

OHOP/Division of Hematology Products:
Ann Farrell, MD, Director
Nicole Gormley, MD, Acting Clinical Team Leader
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Hyon-Zu Lee, Pharm D, Clinical Reviewer
Lori Ehrlich, MD, PhD, Medical Officer
Tamy Kim, PharmD, Associate Director of Regulatory Affairs
Rachel McMullen, MPH, Regulatory Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Gene Williams, PhD, Clinical Pharmacology Team Leader
Christy John, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/ Office of New Drug Products
Okpo Eradiri, PhD, Acting Biopharmaceutics Team Leader

SPONSOR ATTENDEES

Addmedica
Isabelle Dupuis, Pharm.D, Executive Director, Regulatory Affairs
Corinne Duguet, MD, Medical Director
Bernard Dauvergne, Pharm D Executive Director

Voisin Consulting Inc.
David Lucking, BSc, Senior Director
Nathalie Boeglin, Pharm.D, Director, Regulatory Sciences

1.0 BACKGROUND

Siklos® (hydroxycarbamide), is being developed by Addmedica SAS for the following indication: *to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatrics from 2 years old with sickle cell anemia with recurrent moderate to severe painful crises including acute chest syndrome*. Hydroxyurea (HU) or hydroxycarbamide (international non-proprietary name) is an antineoplastic drug that has been marketed worldwide for several decades. Addmedica has developed a proprietary formulation of HU, i.e. a 1000 mg scored film-coated tablet and a 100 mg film-coated tablet which allow flexible dosing in 100 mg and 250 mg intervals to meet the specific needs of Sickle Cell Anemia (SCA) patients, specifically young patients. Siklos® was designated by the FDA as an orphan product for the treatment of Sickle Cell Disease in patients under 18 years on July 24, 2013.

A pre-NDA meeting was held on December 11, 2014 to discuss the legal basis for Siklos® and the New Drug Application (NDA) data package to support market registration in the United States. The Sponsor intends to submit a New Drug Application (NDA) for Siklos® 100 and 1000 mg hydroxyurea (HU) or hydroxycarbamide (international non-proprietary name) film-coated tablets by the end of 2015.

On August 11, 2015, Addmedica SAS requested a Type C meeting to discuss CMC and clinical data content for the NDA submission.

FDA sent Preliminary Comments to Addmedica on October 19, 2015.

2.0 DISCUSSION

Chemistry, Manufacturing and Controls Questions:

Question 1: *Addmedica has developed a new HPLC method for the assay of* (b) (4) *and related substances in the finished product. The quality of analysis is improved : better peak shape for our compounds and a greater efficiency with better selectivity and the introduction of limits of detection and quantification for the identified related substance, hydroxylamine whereas the previous HPLC method allowed just a limit test. Addmedica intends to ask for 36 months shelf life based on 36 months real time stability data with the previous HPLC method and 3*

months 40°C 75% HR with the new one at time of submission. Does the Agency agree with this approach?

FDA Response:
Your approach seems reasonable if the HPLC assay method is stability indicating and all quality attributes are within the justified limits of the acceptance criteria. Therefore, the stability data including the analytical methods need to be reviewed prior to granting the shelf life. For Phase 2 and Phase 3 IND CMC guidance please follow:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf

For a Phase 1 IND guidance, please follow:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf

***DISCUSSION*: There was no discussion.**

***Question 2:** With the available stability data one of the degradation products is identified by the RTT and reaches (b)(4)% at shelf-life. Is it acceptable?*

FDA Response:
No. All degradation products are recommended to be reported, identified and qualified according to the ICH Q3B(R2). You may find the threshold of degradation products at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073389.pdf

***DISCUSSION*: There was no discussion.**

***Question 3**: One of the degradation products can reach the threshold of (b)(4)% which can mean the need of identification and quantification according to ICH Q3b.*

(b)(4)

FDA Response:
No. We recommend that you follow ICH Q3B (R)2 for reporting, identification and qualification. However, your justification may be considered during the NDA review.

***DISCUSSION*: There was no discussion.**

***Question 4**: The API is controlled upon receipt by the manufacturing site taking into account the European and the US Pharmacopeia. Both monographs are close but slightly differ for some methods such as water content or IR spectrum. The sponsor is considering not duplicating tests as explained below. Is it acceptable?*

FDA Response:
Yes. However, all the CMC information, including method descriptions, must be reported in the proposed NDA or be cross-referenced to a DMF. With regards to using a reference spectrum obtained with the USP standard generated once and used for comparison purposes for future batches, this approach could be acceptable, but will require on-site evaluation for its implementation.

DISCUSSION**: There was **no discussion.

***Question 5**: At receipt the active substance and the sodium stearyl fumarate are tested by the drug product manufacturing site according to the USP and the EP related monographs. The Sponsor will perform every test using the USP once for every component and intends to perform the related substances tests using onwards the EP method which provides more precise testing, without further analytical validation. Is it acceptable for the Agency?*

FDA Response:
Yes. However, we recommend that you include control strategies for functional properties of drug substance and all excipients including stearyl fumarate in your proposed NDA.

***DISCUSSION**: There was no discussion.*

***Question 6**: The immediate release tablets of Siklos® 1000mg have a functional score.* (b) (4) [redacted]

FDA Response:
(b) (4) [redacted]

***DISCUSSION**: There was no discussion.*

Clinical Questions:

***Question 7:** Following the pre-NDA meeting, Addmedica planned to submit the Ferster randomised, double-blind, placebo-controlled study in children with SCA (Ferster, Vermylen et al. 1996) in support of licensing Siklos® for patients under 18 years of age in the US.*

(b) (4)

FDA Response:

No. (b) (4)

(b) (4)

DISCUSSION:

The Sponsor suggested using, as their pivotal study, their ongoing prospective cohort study, European Sickle Cell Disease Cohort-Hydroxyurea (ESCORT-HU)-please refer to the Sponsor's hand-out attached to these minutes. The Sponsor asked about the acceptability of this approach. The Agency stated that it would be difficult to comment on the acceptability of this approach without reviewing a more complete proposal. The Agency requested that the Sponsor submit to the IND a proposal that outlines the following:

- ***Topline efficacy and safety results for ESCORT-HU***
- ***Proposal for the statistical analysis, including handling of missing data***
- ***Proposal for endpoints to be used to support approval***
- ***Further description of the baseline information collected, amount of missing data, and processes in place to verify accuracy of data.***
- ***Publications to be included in the submission as supportive data***

The Sponsor offered to submit a blank CRF with the proposal.

(b) (4)

Question 8: (b) (4)

(b) (4)

FDA Response:
No. See our response to Question #7.

DISCUSSION: ***There was no discussion.***

Question 9: (b) (4)

FDA Response:
No, (b) (4)

DISCUSSION: ***There was no discussion.***

3.0 OTHER IMPORTANT MEETING INFORMATION:

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to

conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's presentation is attached.

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NICOLE J GORMLEY
10/30/2015

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	June 14, 2016; 1:00 PM – 2:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	PIND 124532
Product Name:	Siklos (hydroxyurea)
Indication:	Sickle Cell Anemia
Sponsor/Applicant Name:	Addmedica SAS
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

OHOP/Division of Hematology Products:
Ann Farrell, MD, Director
Nicole Gormley, MD, Acting Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Rachel Ershler, MD, MHS, Medical Officer
Patricia Dinndorf, MD, Clinical Reviewer
Kris Kolibab, PhD, Senior Regulatory Project Manager

Division of Hematology Oncology Toxicology Staff:
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Office of Biostatistics:
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Lola Luo, PhD, Statistical Reviewer

SPONSOR ATTENDEES
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Corinne Duguet, MD, Medical Director
Bernard Dauvergne, PharmD, Executive Director

Consulting Team:
David Lucking, BSc, Senior Director, Voisin Consulting, Inc., US Agent
Nathalie Boeglin, PharmD, Director, Voisin Consulting
(b) (4)

1.0 BACKGROUND

Siklos® is being developed by Addmedica SAS for the following indication: *to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatrics from 2 years old with sickle cell anemia with recurrent moderate to severe painful crises including acute chest syndrome*. Hydroxyurea (HU) or hydroxycarbamide (international non-proprietary name) is an antineoplastic drug that has been marketed worldwide for several decades. Addmedica has developed a proprietary formulation of HU, i.e. a 1000 mg scored film-coated tablet and a 100 mg film-coated tablet which allow flexible dosing in 100 mg and 250 mg intervals to meet the specific needs of Sickle Cell Anemia (SCA) patients, specifically young patients. Siklos® was designated by the FDA as an orphan product for the treatment of Sickle Cell Disease in patients under 18 years on July 24, 2013.

FDA sent Preliminary Comments to Addmedica SAS on June 10, 2016.

2. DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: Addmedica intends to include in Module 3 a description of the 100 mg scored tablet and to provide 1 month stability data and data to support the functional score upon availability during the NDA review. Does the Agency agree with this approach and that the submission of these data will not extend the review time?

FDA RESPONSE:
No, we recommend that you submit the stability data for the scored 100 mg tablet and the data to support the functional score in your proposed original NDA. You may update the stability data for the scored tablet during the NDA review.

We are concerned about dividing a 1000 mg film coated tablet by hand into four equal parts considering the dosing errors that may occur when the drug product reaches the market. You may consider developing separate dosage strengths instead. You may also consult "Tablet scoring: Nomenclature, Labeling and Data for Evaluation" guidance which is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

CM269921.pdf". The USP <705> and Ph.Eur 0478 are generally recommended for testing two halves of a scored split uncoated tablet.

The stability data for all proposed commercial configurations are recommended to be generated for shelf life determination. The primary stability batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

Where possible, batches of the drug product should be manufactured by using different batches of the drug substance. Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied. Other supporting data can be provided.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping). For additional guidance on stability studies please follow the ICH stability guidance which can be found at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf.

Discussion:

The Sponsor indicated that the scored 100mg tablet will not be included in the NDA and the scored 1000mg will be included in the NDA and it should meet the Agency's criteria as outlined in the guidance.

Question 2: Does the FDA agree that the format and content of the NDA as described in the pre-NDA briefing package is acceptable for the submission of the NDA, the filing of the NDA by the FDA, and the subsequent approval of Siklos® for the proposed indication?

FDA RESPONSE:
The proposed format and content are acceptable for submission of the NDA. However, the filability and subsequent approval of the NDA will be a review issue.

You should include the results of a food effect study in the original NDA submission. You should provide a detailed summary of the clinical pharmacology information you plan to use from the listed drug.

In addition, if you plan to use published literature as supportive evidence of the pharmacokinetics of your drug product, you should provide adequate information in the original

NDA submission for the Agency to evaluate the scientific bridge between the drug products used in these references and your drug product.
From a technical standpoint (not content related) yes, the proposed format of the submission is acceptable. However, please see additional comments, below.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

- Regarding use of the m5-3-7 heading element, FDA doesn't use module 5.3.7 CRFs. Case Report Forms need to be referenced in the appropriate study tagging file (STF) of the study to which they belong, organized by site as per the specifications and tagged as "case report form".

Your options for cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (e.g. non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.
To use the second option (i.e. cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g xlink:href="../../**ind900000**/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to IND XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Discussion:

The Agency recommended the Sponsor conduct a food effect study before submitting the original NDA submission. The Agency provided general advice regarding patient population and study design and referred the Sponsor to the guidance.

The Agency stated that it is acceptable to list in modules 5.2 and 2.7.6, only the clinical studies for which a clinical study report is provided.

It is also acceptable for the Sponsor to cross-reference information in the Droxia label.

Question 3: Does the FDA agree that the format and content of the proposed prescribing information for Siklos® is adequate to support the submission of the NDA, the filing of the NDA by the FDA, and the subsequent approval of Siklos® for the proposed indication?

FDA RESPONSE:

Overall, the proposed prescribing information is acceptable for submission of the NDA. Specific formatting and content will be decided during labeling negotiation. Also see response to question #2.

Since this is a non-interventional cohort study and not adequately designed for inferential comparisons, the statistical results may be considered exploratory. Whether or not any inferential claims can be included on the label will be a review issue.

We noticed that two different definitions for the Value at least 6 months after initiation of Siklos® are defined and have not been agreed upon. Hence, more exploratory analyses should be provided to show and explain the robustness of efficacy results in terms of different defined windows. Which definition is appropriate to use will be a review issue.

The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.

Discussion:

The Sponsor clarified the difficulty of obtaining complete data in observational studies. Due to the concern of measurement variability, the Agency recommends further exploratory analyses to be provided.

Question 4: Does the FDA agree that the format and content of the Integrated Summary of Efficacy (ISE) for Siklos® is adequate to support the submission of the NDA, the filing of the NDA by the FDA, and the subsequent approval of Siklos® for the proposed indication?

FDA RESPONSE:

The proposed format and content of the ISE are acceptable to support the submission of the NDA. However, we have the following comments:

- In table 5 (ESCORT-HU Biological Efficacy) of the meeting package, the number of patients decreased from 61 patients at baseline to 47 patients post-baseline in the analysis of "HbF (%) at least 6 months after initiation of Siklos" and from 33 patients at baseline to 22 patients post-baseline in the "HbF (%) at 6 months after initiation of Siklos"

analysis. Missing data will be a review issue. Provide clarification of the differences in the number of patients analyzed.

- Similarly, in table 6 (ESCORT-HU Clinical Efficacy), the numbers of patients differ in the analysis of painful crisis, hospitalization and blood transfusion "prior enrollment" and "value during the first year or treatment with Siklos". Missing data will be a review issue. Provide clarification.

Discussion:

The Sponsor provided additional breakdown of the available patient data they expect to have. The Sponsor plans to conduct analysis primarily on the patients with both baseline and post-baseline data. Additionally, the Sponsor will evaluate the characteristics of those patients with missing data. The Agency stated that this proposal appears acceptable.

Question 5: Does the FDA agree that the format and content of the Integrated Summary of Safety (ISS) for Siklos® is adequate to support the submission of the NDA, the filing of the NDA by the FDA, and the subsequent approval of Siklos® for the proposed indication?

FDA RESPONSE:
The format and content of the ISS are acceptable to support the submission of the NDA. However, with regards to patient narratives in the CSR of the ESCORT-HU trial, please include patient narratives for deaths within 30 days of the last dose of study treatment, SAEs, AEs leading to treatment discontinuation and AEs of special interests.

Discussion:

The Sponsor proposes to include in the data set all adverse events and will flag those that are disease related or treatment related. The sponsor also proposes to include narratives for non-SCD related SAEs including infection, AEs leading to discontinuation, AEs of special interest and deaths. The Agency requested that any additional narratives that are requested be submitted sooner than the proposed 30 day timeframe.

Question 6: Addmedica intends to include a Medication Guide to assure safety use of Siklos® in the NDA. Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not required for Siklos®?
FDA RESPONSE:

At this time, there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary. This will be determined during the review of your application.

Discussion:

No discussion occurred.

Regulatory
Question 7: Does the Agency agree that a NDA in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act is appropriate for Siklos®?

FDA RESPONSE:
Yes.

Discussion:

No discussion occurred.

Question 8: Does the Agency agree that the NDA for Siklos® will likely qualify for priority review?

FDA RESPONSE:
The review priority will be decided at the time of filing. You should submit your justification for priority review with the NDA submission.

Discussion:

No discussion occurred.

Question 9: In order to obtain pediatric exclusivity for Siklos®, would FDA need to issue a Written Request (WR) before submission of the NDA? If the NDA is approved and FDA issues a WR, is it possible for the WR to cover only the studies that have already been completed, upon which approval was based? Or, by definition, does the WR have to include a new study (ies) either in the same population covered by the NDA (2-17 years) or in the younger population?

FDA RESPONSE:
Siklos has been granted orphan drug designation for the treatment of sickle cell disease in patients under 18 years of age. If you are the first sponsor to receive marketing approval for hydroxyurea for the above orphan designation indication, you are eligible for orphan exclusivity for the approved indication.

Pediatric Exclusivity is separate from Orphan Drug Exclusivity. Pediatric Exclusivity adds 6 months to existing Patents/Exclusivity. Pediatric Exclusivity is granted in response to a Written Request (WR). If you want to be considered for Pediatric Exclusivity, you should submit a Proposed Pediatric Study Request (PPSR) to the IND prior to submission of the NDA. FDA will consider issuing a WR in response to the PPSR. FDA cannot issue a WR for a study that has been submitted to the FDA. See Guidance for Industry Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.

Discussion:

With regards to the Sponsor submitting a PPSR and FDA issuing a written request before the NDA filing, the Agency stated that the Sponsor will be eligible for pediatric written request.

The Agency stated that they will provide a definitive answer to the second question in the post-meeting comment.

Post-Meeting Comment:
A 505(b)2 application could be eligible for pediatric exclusivity in the setting in which new clinical studies were submitted in response to a pediatric Written Request. After the reports on the requested pediatric studies are completed and submitted within the requested time, FDA will determine whether the studies were conducted in accordance with the Written Request thus qualifying for pediatric exclusivity.

As part of a Written Request, there would need to be an age appropriate formulation for all patients that would be treated. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation.

Also, in accordance with section 505A(e)(2), if

1) **you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);**
2) **the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and**
3) **you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.**

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

For additional information regarding Pediatric Exclusivity, please refer to the following website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm

3.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slide deck for the meeting.

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/s/

NICOLE J GORMLEY
06/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 124352

MEETING MINUTES

addmedica SAS
c/o Voisin Consulting, Inc. Life Sciences
Attention: Jessica E. Foley, MS, RAC
Director, Regulatory Drugs/Biologics
222 Third Street, Suite 3121
Cambridge, MA 02142

Dear Ms. Foley:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Siklos® (hydroxycarbamide).

We also refer to the meeting between representatives of your firm and the FDA on Thursday, December 11, 2014. The purpose of the meeting was to discuss the legal basis for Siklos® and the New Drug Application (NDA) data package to support market registration in the United States.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Thursday, December 11, 2014; 1:00PM - 2:00PM EST
Meeting Location:	FDA White Oak Federal Research Center 10903 New Hampshire Avenue White Oak Bldg 22, Room 1315 Silver Spring, MD 20903
Application Number:	PIND 124352
Product Name:	Siklos® (hydroxycarbamide)
Indication:	Treatment of Sickle Cell Anemia in children
Sponsor/Applicant Name:	addmedica SAS
Meeting Chair:	Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Meeting Recorder:	Rachel McMullen, MPH, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Gregory H. Reaman, MD, Associate Director for Oncology Science
Tamy Kim, PharmD, Associate Director of Regulatory Affairs
Erik Laughner, MS, RAC, Regulatory Scientist

OHOP/Division of Hematology Products:
Ann Farrell, MD, Director
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Hyon-Zu Lee, Pharm D, Clinical Reviewer
Rachel McMullen, MPH, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Acting Team Lead
Pedro Del Valle, PhD, Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Acting Team Leader
Sarah Schrieber, PharmD, Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment/Division of New Drug Quality Assessement I
Janice Brown, MS, CMC Lead
Xiao-Hong Chen, PhD, Product Quality Reviewer
Angelica Dorantes, PhD, Biopharmaceutics Team Leader
Salaheldin Hamed, PhD, Biopharmaceutics Reviewer

SPONSOR ATTENDEES

addmedica SAS
Isabelle Dupuis, PharmD, Executive Director, Regulatory Affairs
Corinne Duguet, MD, Medical Director
Bernard Dauvergne, PharmD, Executive Director

Voisin Consulting, Inc.
Anya Harry, MD, Medical Director
Jessica E. Foley, MS, RAC, Director, Regulatory Drugs/Biologics

1.0 BACKGROUND

On October 10, 2014, 2014, addmedica SAS requested a Pre-NDA meeting to discuss the legal basis for Siklos® and the New Drug Application (NDA) data package to support market registration in the United States.

On December 9, 2014, FDA provided addmedica SAS with preliminary meeting responses to the questions contained in their November 7, 2014 meeting package.

2.0 DISCUSSION

2.1 CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Question 1: Addmedica plans present data to support USP quality standard of the API in the NDA submission, therefore no drug master file (DMF) will be referenced and no Letter of Authorization will be included in the dossier. Does the Agency agree with this approach?

FDA Response:
No. The Agency does not agree with your approach. Complete CMC information for (b) (4) drug substance should be submitted in the NDA. Alternatively, this information can be submitted by referencing a Type 2 DMF.

DISCUSSION:
There was no discussion.

Question 2: In Module 3 of the NDA, sections for the two strengths (100 mg and 1,000 mg) will be combined when both strengths share a common description. However for the ease of review and future submission maintenance activities, sections where differences exist (e.g.,

3.2.P.7) will be separated based on the two strengths. Does the Agency agree with this approach?

FDA Response:
Your approach is acceptable.

DISCUSSION:
There was no discussion.

Question 3: Addmedica has assigned an expiry date of 36 months to both strengths of the drug product based on the stability data from normal and accelerated conditions for the 100 mg and 1,000 mg Siklos® batches. Does the Agency agree with this approach?

FDA Response:
Determination of acceptability for the proposed expiry date will be made at the NDA review when complete CMC information has been evaluated. Regarding the stability studies, please refer to the ICH Q1A, Q1B, Q1C and Q1E guidance documents.

Additional CMC Comments:

- **The acceptance criteria for the drug product shelf life specifications should be the same as those of the release specifications. The drug product is expected to conform to the regulatory (release and stability) specifications from release through its shelf life.**

- **Use USP compendial analytical methods for the drug product regulatory specification, e.g., Uniformity of Dosage Units per USP<905>.**

- **Include test for water content in the drug product regulatory specification.**

- **The drug product primary stability studies should be conducted with the drug product batches manufactured by the proposed commercial process and packaged in the proposed commercial packaging system, e.g., same HDPE bottles, same tablet counts and same packaging conditions (with or without desiccant), etc.**

DISCUSSION:
There was no discussion.

Question 4: Does the Agency agree that the sampling process used during process validation is acceptable for the 100 mg and 1000 mg Siklos® tablets?

FDA Response:
It is the company's responsibility to comply with CGMP sampling requirements during process validation stage 2, process performance qualification: samples must represent the batch under analysis (§ 211.160(b); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)). The sampling and analysis need to ensure that no

significant differences exist between in-process locations that could adversely affect finished product quality. Further, within-location variability (between samples within a given sampling location) should be evaluated as it is critical to demonstrate that variability attributable to sample location is not significant. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch.

FDA does not review or approve proposed approaches for process validation. The actual sampling plan, acceptance criteria and statistical analysis will be evaluated during an inspection. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices (January 2011) at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

Please note that FDA withdrew its draft guidance for industry on "*Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment*" (November 2003). Please refer to *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Production and Process Controls* for information on the withdrawal of the draft guidance at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#15.

DISCUSSION:
There was no discussion.

2.2 NON CLINICAL

Question 5: Does the Agency agree that the current non-clinical package for Siklos® is sufficient to support an NDA, and that no additional nonclinical study is needed?

FDA Response:
No. An assessment of the potential toxicological effects on reproductive function induced by the long-term use of (b) (4) in the pediatric population should be included in your submission. The assessment should also address the potential for toxicity over multiple generations, considering the effects of prenatal and postnatal exposures to (b) (4) on postnatal development, including the potential for developmental neurotoxicity, reproductive function, and carcinogenicity.

DISCUSSION:
The Agency recommends the Sponsor to provide in detail, a written and tabulated summary for the non-clinical section of the NDA, which covers the assessment of the

potential toxicological effects of (b) (4), as described in the FDA response above.

2.3 CLINICAL

Question 6: Does the Agency agree that the current clinical package for Siklos® is sufficient to support an NDA, and that no additional clinical study is needed?

FDA Response:
No. Your proposed listed drug (LD), Droxia, does not have a pediatric indication. To seek an indication in patients under 18 years of age, you will need to conduct pivotal trials and demonstrate substantial evidence of safety and effectiveness. The submission should include full study reports and datasets. Your complementary clinical data derived from studies and updates of registries in pediatric patients and the ESCORT-HU trial may be submitted in the NDA to support safety.

The need for a dedicated food effect study, dedicated renal and/or hepatic impairment studies, and *in vitro* cytochrome P450 enzyme metabolism studies will be a review issue.

DISCUSSION:
The Sponsor will submit more details including the statistical analysis plan (SAP), on their proposal to provide data from the clinical trials listed in Table 1 of their document. The Sponsor should include adequate information and justifications to address each of the clinical pharmacology aspects in the NDA submission. The Sponsor stated that a renal study is ongoing.

For the sickle cell adult indication, a 505(b)(2) pathway referencing Droxia would be acceptable. The Sponsor needs to provide information on the linearity of the PK at the highest dose strength of the listed and proposed drug.

Question 7: Does the Agency agree that Droxia® is the appropriate reference listed drug (RLD) and that a bioequivalence study comparing Siklos® to Droxia® is not required for the registration of Siklos® in the US?

FDA Response:
The Agency typically does not advise a Sponsor on the selection of a particular LD that may be relied on for a 505(b)(2) application. However, the proposed LD appears to be acceptable only for seeking the current Droxia indication. See our response to question #6.

Regarding the study that you have already conducted, be aware that Sickle Cell Anemia (SCA) is not an indication in the labeling of Hydrea 500 mg. The LD you have used in the BA/BE study is therefore inappropriate. The highest strength of your proposed drug product should be bridged to the appropriate LD which must have the same indication for which you seek approval, that is, Sickle Cell Anemia (SCA) in children.

A biowaiver may be requested for the lower strength. However, note that at present, there is no LD product indicated for treatment of SCA in children in the US.

DISCUSSION:
Refer to the discussion for question 6.

Question 8: Does the Agency agree that the requirement for the provision of the Integrated Summary of Safety (ISS) and Integrated Summary of Effectiveness (ISE) in the NDA for Siklos® can be waived?

FDA Response:
See our response to question #6.

DISCUSSION:
For the adult indication an ISS/ISE would not be needed. However, for the pediatric indication, an ISS/ISE would be required.

2.4 REGULATORY

Question 9: Does the Agency agree that the NDA for Siklos® will likely qualify for priority review?

FDA Response:
See our response to question #6.

DISCUSSION:
There was no discussion.

Question 10: Does the Agency agree that an NDA in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act is appropriate for Siklos®?

FDA Response:
Refer to our response to questions #6 and #7.

Also see our detailed recommendations below under 505(b)(2) REGULATORY PATHWAY for the proposed 505 (b)(2) application.

DISCUSSION:
The Agency recommends that the Sponsor consider the available literature.

Question 11: Does the Agency agree that the NDA for Siklos® will likely qualify for pediatric exclusivity and that a Proposed Pediatric Study Request (PPSR) from addmedica is not required?

FDA Response:
Your question regarding exclusivity is premature as all exclusivity determinations are made after approval. For additional general information regarding drug product exclusivity, please refer to the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm.

As Siklos was designated by the FDA as an orphan product for the treatment of SCD in patients under 18 years and if this is the only indication you are currently pursuing, PREA does not apply.

DISCUSSION:
The Agency recommends that the Sponsor submit their proposals to the PIND for Agency review.

Question 12: Should addmedica decide to expand the claimed indication to include adults, would Siklos® still be eligible to obtain orphan exclusivity in the pediatric population if the NDA is approved?

FDA Response:
Yes, the Sponsor would be eligible for orphan exclusivity for pediatric patients (0-16) and adolescent patients up to the age of 18.

DISCUSSION:
The Sponsor would need to amend the current orphan drug designation in order to receive the designation for adults with SCD. Please consult OOPD prior to submitting the request.

Question 13: Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not required for Siklos®?

FDA Response:
No. Please see our response to question #6. We cannot make a determination for the need for a REMS without reviewing the trial safety data.

DISCUSSION:
There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION:

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and

each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses to FDA Preliminary Comments are attached.

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/s/

VIRGINIA E KWITKOWSKI
12/19/2014