CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216157Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 Memorandum:	December 15, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216157 and NDA 213137/S-006
Product Name and Strength:	Oxbryta (voxelotor) NDA 216157: Tablets for oral suspension, 300 mg NDA 213137/S-006: Tablet, 500 mg
Applicant/Sponsor Name:	Global Blood Therapeutics, Inc.
OSE RCM #:	2021-1269-3 and 2021-1299-3
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 9, 2021 for Oxbryta. We reviewed the revised container labels to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made to revise the storage information in the Prescribing Information[a].

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Thompson, C. NDA 213137S006 and NDA 216157 Labeling Information Request for Oxbryta (NDA 216157 and NDA 213137/S-006). Silver Spring (MD): FDA, CDER, OND, DNH (US); 2021 DEC 08.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 Memorandum:	December 2, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216157 and NDA 213137/S-006
Product Name and Strength:	Oxbryta (voxelotor) NDA 216157: Tablets for oral suspension, 300 mg NDA 213137/S-006: Tablet, 500 mg
Applicant/Sponsor Name:	Global Blood Therapeutics, Inc.
OSE RCM #:	2021-1269-2 and 2021-1299-2
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on November 29, 2021 for Oxbryta. We reviewed the revised container labels 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] and memorandum[b].

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a]Karpow, C. Label and Labeling Review for Oxbryta (NDA 216157 and NDA 213137/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 03. RCM No.: 2021-1269 and 2021-1299.
[b] Karpow, C. Label and Labeling Memorandum for Oxbryta (NDA 216157 and NDA 213137/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 22. RCM No.: 2021-1269-1 and 2021-1299-1.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 Memorandum:	November 22, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216157 and NDA 213137/S-006
Product Name and Strength:	Oxbryta (voxelotor) NDA 216157: Tablets for oral suspension, 300 mg NDA 213137/S-006: Tablet, 500 mg
Applicant/Sponsor Name:	Global Blood Therapeutics, Inc.
OSE RCM #:	2021-1269-1 and 2021-1299-1
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on November 9, 2021 for Oxbryta. We reviewed the revised container labels 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 are unacceptable from a medication error perspective. The prominence of the statement, "Tablets MUST be dispersed in water or clear liquid prior to ingestion." and the location of the net quantity statement can be improved.

[a] Karpow, C. Label and Labeling Review for Oxbryta (NDA 216157 and NDA 213137/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 03. RCM No.: 2021-1269 and 2021-1299.

3 RECOMMENDATIONS FOR GLOBAL BLOOD THERAPEUTICS, INC.

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

A. Container labels

a. The statement, “Tablets MUST be dispersed in water or clear liquid prior to ingestion.” is not prominent and we are concerned this statement may be overlooked which may result in wrong preparation medication error. We recommend you make this statement more prominent by bolding the statement and using a different color font or by other means.

b. The net quantity is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement the away from the product strength, such as the left corner of the principal display panel.

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CLINICAL INSPECTION SUMMARY

Date	November 5, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Patricia Oneal, Medical Officer Tanya Wroblewski, M.D., Team Leader Ann Farrell, Division Director Caden Brennen, M.S., Regulatory Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
NDA	NDA 216157 and NDA 213137/S-06
Applicant	Global Blood Therapeutics, Inc.
Drug	Oxbryta® (voxelotor)
NME	No
Division Classification	Hemoglobin S polymerization inhibitor
Proposed Indication	Treatment of children four years or older with sickle cell disease.
Review Type	Priority
Consultation Request Date	July 17, 2021
Summary Goal Date	November 10, 2021
Action Goal Date	December 10, 2021
PDUFA Date	December 25, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study (GBT440-007) were submitted to the Agency in support of New Drug Applications (NDA 216157 and NDA 213137 S-06) of the drug voxelotor for treatment of children four years or older with sickle cell disease. Two clinical investigator sites (Jeremie Estepp, M.D. and Robert Clark Brown, M.D., Ph.D.) were inspected in support of the application submission to the Agency.

Based on these inspections, the data generated from the above investigator sites appear reliable without significant regulatory violations noted. Study GBT440-007 submitted to the Agency appear acceptable in support of the proposed indication.

II. BACKGROUND

Voxelotor (Oxbryta®) is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state. Voxelotor (GBT440) tablets for oral use, 500 mg, was granted accelerated approval on November 25, 2019 for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older under New Drug Application (NDA) 213137.

In current the application, the sponsor submitted NDA 213137/S-06 with an ongoing Phase 2a clinical Study GBT440-007 to support an extension of the accelerated approval of Oxbryta for the treatment of SCD in pediatric patients 4 to 11 years of age. At the same time, the sponsor also submitted NDA 216157 formulated as Oxbryta tablets for oral suspension, 300 mg (also referred to as dispersible tablets) as a new, age-appropriate and weight-based dosage form to support the extension of the pediatric population.

Study GBT440-007

Study GBT440-007 is an ongoing Phase 2a, multicenter, open-label study of voxelotor in pediatric subjects with sickle cell disease. The study is composed of 4 parts (Parts A, B, C, and D). Parts A and B have been completed, and results were submitted in 2019. The current clinical study report included results from Part C of the study.

Following a 35-day screening period, eligible subjects returned to clinic on Day 1 to receive their first dose of study drug and then were to return for study visits at Weeks 2, 4, 8, 12, 16, 20, 24, 36, and 48, as well as for an end of study visit (4 weeks after the last dose of study drug for subjects who do not enroll into the open-label extension study [Study GBT440-038]). Assessments performed at each study visit were in accordance with the Schedule of Assessments for Part C. Part C of the study was designed to last approximately 57 weeks, including the 35-day Screening Period, the 48-week Treatment Period, and the end of study Visit (4 weeks after the last dose of study drug for subjects who do not enroll into the open-label extension study.

The primary objectives of the study were (1) to characterize the plasma and whole blood pharmacokinetics of voxelotor following multiple doses in pediatric subjects with sickle cell disease, (2) to evaluate the effect of voxelotor on clinical measures of anemia and hemolysis, (3) to evaluate the effect of voxelotor on cerebral hemodynamics as measured by transcranial doppler flow velocity, and (4) to evaluate the safety and tolerability of voxelotor following multiple doses in pediatric patients with sickle cell disease.

The primary efficacy outcomes were: (a) hemoglobin response at Week 24, (b) change from baseline to Week 24 in hemoglobin, (c) percent change from baseline to Week 24 in indirect bilirubin, percent reticulocyte count, and lactate dehydrogenase and (d) change from baseline to Week 24 in cerebral blood flow as measured by the time-averaged mean of the maximum transcranial doppler flow velocity.

As of data cutoff date of September 2020, a total of 56 pediatric subjects had been treated with voxelotor in Part C, including 45 pediatric s subjects aged 4 to 11 years and 11 pediatric subjects aged 12 to 17 years. Part C is ongoing.

Two clinical investigator sites were selected for inspection based on the high numbers of enrolled patients.

III. RESULTS (by site)

1. **Jeremie Estepp, M.D. / GBT440-007 (IND 121691)/Site #01-1015**
   St. Jude Children's Research Hospital
   262 Danny Thomas Place, Mail Stop 800
   Memphis, TN 38105

   Inspection dates: August 31 to September 2, 2021

   A total of 9 study subjects were screened and six study subjects were enrolled, randomized, and received study treatment. Three patients completed the study phase through Week 48, and three study subjects discontinued due to drug intolerance.

   Records reviewed included but were not limited to the following: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, case report forms, subject source records, protocol adherence, test article control records, and adverse event/serious adverse event documentation.

   Source records for six randomized study patients at the site were reviewed and compared with the submitted data listings for the site. Source document consisted of paper forms, print-out of electronic medical records, paper copies of laboratory reports, questionnaire and subject responses, and progress report notes.

   The primary and secondary efficacy endpoint data in the source records were verified against the data in submitted patient line listings. No discrepancies were noted. No under-reporting of adverse events noted.

2. **Robert Clark Brown, M.D., Ph.D. /GBT440-007 (IND 121691)/Site #01-1018**
   5461 Meridian Mark Rd., Suite 400
   Atlanta, GA 30342

   Inspection dates: August 9 to 20, 2021

   A total of 23 study subjects were screened and consented. Seventeen study subjects were enrolled, randomized, and 15 patients completed the study. One patient did not complete the study (withdrawal of consent) and one subject is still part of an ongoing study.

Records reviewed involved the following items: IRB approvals and informed consent documentation, screening and enrollment log, monitoring reports, electronic case report forms, subject source records, test article control records, adverse event reporting, regulatory binder containing sponsor and monitor correspondence, drug shipment records, drug shipment accountability, and drug storage temperature records.

Source records for the 15 randomized study patients at the site were reviewed and compared with the submitted data listings for the site. The efficacy data in the source records were verified against the data in the patient line listings. No discrepancies were noted. No under-reporting of serious adverse events or data discrepancies were observed.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	November 3, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216157 and NDA 213137/S-006
Product Name, Dosage Form, and Strength:	Oxbryta (voxelotor) NDA 216157: Tablets for oral suspension, 300 mg NDA 213137/S-006: Tablet, 500 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Global Blood Therapeutics, Inc.
FDA Received Date:	June 25, 2021 and October 22, 2021
OSE RCM #:	2021-1269 and 2021-1299
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Global Blood Therapeutics, Inc. submitted a New Drug Application (NDA) for Oxbryta (voxelotor) tablet for suspension under NDA 216157 to propose a new dosage form, tablets for oral suspension, and efficacy supplement to NDA 213137/S-006 to propose to lower the indicated age limit from 12 years to 4 years in pediatric patients with sickle cell disease (SCD). We evaluated the proposed Oxbryta prescribing information (PI), patient package insert (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

Oxbryta (voxelotor) tablets was approved under NDA 213137 on November 25, 2019 as a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older. Oxbryta (voxelotor) is currently available as 500 mg tablets.

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 Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Global Blood Therapeutics, Inc. is proposing a new strength and dosage form, 300 mg tablets for oral suspension, for Oxbryta (voxelotor) under NDA 216157 and an efficacy supplement under NDA 213137/S-006 to lower the indicated age limit from 12 years to 4 years in pediatric patients with SCD based on data from an ongoing Phase 2a clinical Study GBT440-007 in pediatric patients with SCD. Both the currently approved 500 mg tablet and proposed 300 mg tablets for oral suspension will have the same PI.

We performed a risk assessment of the proposed PI, PPI, and container label for Oxbryta (voxelotor) to identify areas of vulnerability that may lead to medication errors and other areas for improvement. We note, Section 2, Dosage and Administration presents the recommended dosage in adults and pediatric patients (b) (4). The presentation (b) (4) may cause confusion. Therefore, we recommend (b) (4) for presenting the dosage information for pediatrics and adults.

Section 2.4 of the USPI describes multiple steps to correctly prepare the 300 mg tablets for oral suspension. We note the 300 mg tablets for oral suspension are proposed to be dispensed without an Instructions For Use (IFU) or carton with preparation instructions and we are concerned the applicable preparation instructions in Section 2.4 of the PI would not be provided to patients and caregivers which might lead wrong technique medication error. Therefore, we discussed with the review team and determined the product should have an IFU so that patients and caregivers will have appropriate preparation instructions. The Agency sent an information request (IR) to the sponsor to develop an IFU document for distribution with the tablets for oral suspension and a plan to ensure the IFU would accompany the product for dispensing since the product is only supplied in a container bottle without a carton as currently proposed. The Applicant submitted an IFU for the proposed tablets for oral suspension and stated, "to ensure patients receive the IFU with each prescription dispense, GBT has put in place the following dispensing plan". The plan consists of a single piece of topsert folded and affixed to the container bottle which includes a PI, PPI, and IFU. In addition, specialty pharmacies will have a requirement to provide an IFU with each prescription and include verbal instructions (See Appendix F).

Our review of the proposed PI, IFU, PPI, and container label identified areas that may be revised to improve clarity and readability of important information. We provide recommendations for the Division and the Applicant to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed Oxbryta PI, IFU, PPI, and container label may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below.

RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. Highlights of Prescribing Information
    a. Consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.
2. Dosage and Administration Section
    a. As submitted, Section 2, Dosage and Administration presents the Recommended Dosage in Adults and Pediatric Patients (b) (4)

[redacted]. We are concerned [redacted] is confusing to readers and might lead to dosing errors. Therefore, we recommend [redacted] and simplifying the dosing tables for the pediatric weight-based dosing [redacted].

b. In the table that appears in section 2.4, the term '[redacted]' is used. This term is vague; therefore we recommend you consider revising [redacted], to read, [redacted].

c. Consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.

B. Instructions for Use

1. The bullet, [redacted]." indicates that Oxbryta tablets for oral suspension can be prepared in a clear drink that is [redacted]; however the PI indicates that the Oxbryta tablets for oral suspension should be dispersed in "[redacted]." Revise the IFU for consistency with the PI.
2. The bullet, [redacted]." bolds only the first several words of the statement. We recommend not bolding "[redacted]" as this is not more important than other information on the IFU.
3. "[redacted]" in the table in [redacted] does not have a comma. We recommend revising this to "[redacted]" for readability.
4. The table in [redacted] does not go beyond [redacted]. The doses presented in the prescribing information go up to 2,500 mg. Thus we recommend adding rows to reflect doses above [redacted] to the table.
5. We recommend moving the sub-bullet "[redacted]" to the step that states to wait for 1 to 5 minutes.

RECOMMENDATIONS FOR GLOBAL BLOOD THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of NDA 216157:

A. Container Labels

1. The established name is not at least half the size of the proprietary name and 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).

2. As currently presented, the new proposed dosage form, tablets for oral suspension, is not prominent on the container label and we are concerned this dosage form may be overlooked and contribute to wrong technique medication errors as it is on separate lines. Therefore, we recommend you increase the prominence of the new proposed dosage form (i.e. placing in a box), tablets for oral suspension, taking into account all pertinent factors, including typography, boxing, contrast, and other printing features.

3. Since the administration of the proposed 300 mg tablets for oral suspension are different than the currently marketed 500 mg tablets, we are concerned patients unfamiliar with the new proposed dosage form, tablets for oral suspension, may erroneously fail to disperse the tablet in water or clear liquid prior to ingestion. Therefore, we recommend adding a statement similar to, "Tablets MUST be dispersed in water or clear liquid prior to ingestion. DO NOT CHEW OR SWALLOW WHOLE." to the principal display panel (PDP).

4. Since the administration of the proposed 300 mg tablets for oral suspension are different than the currently marketed 500 mg tablets, we are concerned patients may erroneously attempt to disperse the 500 mg tablets in water or clear liquid prior to ingestion. Therefore, we recommend you consider adding a statement similar to, "Swallow tablets whole. Do not cut, crush, or chew the tablets" to the PDP of the 500 mg tablets container label.

5. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)." to read "Recommended Dosage: See prescribing information."

6. The drug barcode is often used as an additional verification before drug dispensing and administration; therefore, it is an important safety feature that should be part of the label whenever possible. We request you add the product's linear barcode to each individual container label with sufficient whitespace as required per 21CFR 201.25(c)(2) and 21CFR 201.25(c)(i).

7. As currently presented, the serial number, lot number, and expiration date are absent. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act[a]. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018,

[a] Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

respectively. We recommend you review the guidance to determine if the product identifier requirements apply to your product's labeling.

8. As currently presented, the location of the lot number and expiration date is not specified on the labels. Please specify the location of the lot number and expiration date. In addition, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format of the expiration date you intend to use as a placeholder on your container label. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Oxbryta received on June 25, 2021 from Global Blood Therapeutics, Inc..

Table 2. Relevant Product Information for Oxbryta and the Listed Drug		
Product Name	Oxbryta (NDA 216157)	Oxbryta (NDA 213137 S-6)[b]
Initial Approval Date	N/A (under review)	November 25, 2019
Active Ingredient	voxelotor	
Indication	treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older.	
Route of Administration	oral	
Dosage Form	Tablets for oral suspension	Tablet
Strength	300 mg	500 mg
Dose and Frequency	<u>Recommended dosage:</u> • Adults and pediatric patients 12 years (b) (4) and older: 1,500 mg orally once daily with or without food. • Pediatric patients 4 to less than 12 years: based on body weight. <u>Recommended dosage for severe hepatic impairment (Child Pugh C):</u> • Adults and pediatric patients 12 years (b) (4) and older: 1,000 mg orally once daily. • Pediatric patients 4 to <12 years: based on body weight.	
How Supplied	• <u>500 mg tablet:</u> Bottles of 90 tablets with one desiccant canister • <u>300 mg tablet:</u> Bottles of 60 tablets and bottles of 90 tablets for oral suspension	
Storage	(b) (4)	
Container Closure	polyester coil and child-resistant closure	

[b] Oxbryta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 SEP 10. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213137s000lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 10, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “voxelotor”. Our search identified 1 previous reviews[c], and we considered our previous recommendations to see if they are applicable for this current review.

[c] DeGraw, S. Label and Labeling Review for Oxbryta (voxelotor) (NDA 213137). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 24. RCM No.: 2019-1369.

APPENDIX F. INFORMATION REQUESTS

On October 8, 2021, the DNH sent the following information request (IR) to Global Blood Therapeutics, Inc.:

- https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061c4da&_afrRedirect=1604434445435049

On October 14, 2021, the DMEPA sent the following follow-up information request (IR) to Global Blood Therapeutics, Inc.:

- https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061dd8e&_afrLoop=1604429801923498&_afrWindowMode=0&Adf-Window-Id=w1av8sp0iuf&_afrFS=16&_afrMT=screen&_afrMFW=1576&_afrMFH=880&_afrMFDW=1920&_afrMFDH=1080&_afrMFC=8&_afrMFCI=0&_afrMFM=0&_afrMFR=96&_afrMFG=0&_afrMFS=0&_afrMFO=0

On October 22, 2021, we received the following response from Global Blood Therapeutics, Inc.:

To ensure that patients receive the IFU with each prescription dispense, GBT has put in place the following dispensing plan;

- Each bottle of Oxbryta tablets for oral suspension will include a single piece of topsert folded and affixed to its lid. The single topsert will include a PI, a PPI, and an IFU. The layout will allow patients to cut off the IFU without impacting the PI or the PPI. A cut-off line with an appropriate pictogram will be included for patients convenience.
- Additionally, the Specialty Pharmacies (SPs) Contract of services will include a requirement that the SPs provide an IFU with each Oxbryta tablets for oral suspension prescription dispense and verbally review with the patient the preparation and administration steps per the IFU and inform the patient that an IFU will be provided with their prescription order.
- The SPs can print the IFU from the National Drug Compendia (First Data Bank and MediSpan). They will also have the ability to print a stand-alone IFU on demand from a GBT provided approved PDF.

APPENDIX G. LABELS AND LABELING

G.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 Oxbryta labels and labeling submitted by Global Blood Therapeutics, Inc..

- Container labels for proposed 300 mg tablets for oral suspension received on June 25, 2021
- Container label for currently marketed 500 mg tablets, available from http://fdalabel.fda.gov/fdalabel/services/spl/set-ids/3c557fac-29ec-483f-b691-8a935d4decc3/spl-doc?hl=oxbryta
- Prescribing Information (Image not shown) received on June 25, 2021, available from \\CDSESUB1\evsprod\nda213137\0070\m1\us\uspi-redlined.pdf
- Patient Information (Image not shown) received on June 25, 2021, available from \\CDSESUB1\evsprod\nda213137\0070\m1\us\ppi-redline.pdf
- Instructions for Use received on October 22, 2021 \\CDSESUB1\evsprod\nda213137\0092\m1\us\instructions-for-use-oxbryta-dp-clean-18oct2021.pdf

G.2 Label and Labeling Images

Container label – 300 mg, 60 tablets

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

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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 2, 2021
To:	Caden Brennen, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
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:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route, Application Type/Number:	OXBRYTA (voxelotor) tablets, for oral suspension, NDA 216157
Applicant:	Global Blood Therapeutics, Inc.

1 INTRODUCTION

On June 25, 2021, Global Blood Therapeutics Inc. submitted for the Agency's review an original New Drug Application (NDA) 216157 for OXBRYTA (voxelotor) tablets, for oral suspension for the treatment of sickle cell disease in adults and pediatric patients 4 years of age and older. On October 8, 2021, the Division of Non-Malignant Hematology (DNH) requested that the Applicant submit an Instructions for Use (IFU) for the new dosage form, tablets for oral suspension.

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 DNH on October 22, 2021, for DMPP and OPDP to review the Applicant's proposed IFU for OXBRYTA (voxelotor) tablets, for oral suspension.

2 MATERIAL REVIEWED

- Draft OXBRYTA (voxelotor) tablets, for oral suspension IFU received October 22, 2021 and received by DMPP and OPDP on October 22, 2021.
- Draft OXBRYTA (voxelotor) tablets, for oral use and OXBRYTA (voxelotor) tablets, for oral suspension Prescribing Information (PI) received on June 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 25, 2021.

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 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.

In our collaborative review of the IFU we:

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

4 CONCLUSIONS

The IFU is 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 IFU is 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 IFU.

Please let us know if you have any questions.

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BARBARA A FULLER
11/02/2021 11:58:24 AM

LASHAWN M GRIFFITHS
11/02/2021 12:59:30 PM

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:	October 21, 2021
To:	Caden Brennen, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
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:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route, Application Type/Number:	OXBRYTA (voxelotor) tablets, for oral use, NDA 213137/S-006 OXBRYTA (voxelotor) tablets, for oral suspension, NDA 216157
Applicant:	Global Blood Therapeutics, Inc.

1 INTRODUCTION

On June 25, 2021, Global Blood Therapeutics Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 213137/S-006 for OXBRYTA (voxelotor) tablets, for oral use and an original New Drug Application (NDA) 216157 for OXBRYTA (voxelotor) tablets, for oral suspension. With this supplement and original NDA, the Applicant proposes a new dosage form and to lower the indicated age limit from ≥ 12 years of age to ≥ 4 years of age in pediatric patients with sickle cell disease.

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 Non-Malignant Hematology (DNH) on June 30, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OXBRYTA (voxelotor) tablets, for oral use and OXBRYTA (voxelotor) tablets, for oral suspension.

2 MATERIAL REVIEWED

- Draft OXBRYTA (voxelotor) tablets, for oral use and OXBRYTA (voxelotor) tablets, for oral suspension PPI received on June 25, 2021, and received by DMPP and OPDP on October 12, 2021.
- Draft OXBRYTA (voxelotor) tablets, for oral use and OXBRYTA (voxelotor) tablets, for oral suspension Prescribing Information (PI) received on June 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 12, 2021.
- Approved OXBRYTA (voxelotor) tablets, for oral use labeling dated November 25, 2019.

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.

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.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is 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 PPI is 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 PPI.

Please let us know if you have any questions.

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

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

Memorandum

Date: October 22, 2021

To: Caden Brennen, MS, Regulatory Project Manager,
Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for OXBRYTA (voxelotor) tablets, for oral use and OXBRYTA (voxelotor) tablets, for oral suspension

NDA: 213137/Supplement 006 and 216157

In response to DNH's consult request dated June 30, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for OXBRYTA (voxelotor) tablets, for oral use, and for the original NDA submission for OXBRYTA (voxelotor), for oral suspension (Oxbryta). This supplement (S-006) and original NDA are for a new dosage form and to lower the indicated age limit from ≥ 12 years of age to ≥ 4 years of age in pediatric patients with sickle cell disease.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Caden Brennen) on October 12, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 22, 2021, and comments on the proposed IFU will be sent under separate cover at a later time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 25, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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