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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

RICKEY JOLLY, *et al.*, individually and on behalf of others similarly situated,

Plaintiffs,

v.

GLOBAL BLOOD THERAPEUTICS, INC. and PFIZER INC.,

Defendants.

Case No. 3:24-cv-09345-TLT

DEFENDANTS GLOBAL BLOOD THERAPEUTICS, INC. AND PFIZER INC.'S NOTICE OF MOTION AND MOTION TO DISMISS THE FIRST AMENDED COMPLAINT; MEMORANDUM OF POINTS & AUTHORITIES

Date: July 8, 2025
Time: 2:00 PM
Location: Courtroom 9 – 19th Floor
Judge: Hon. Trina L. Thompson

TO THE COURT, ALL PARTIES, AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that on July 8, 2025, at 2:00 p.m., or as soon thereafter as this matter may be heard before the Honorable Trina L. Thompson, Courtroom 9 on the 19th Floor of the United States Courthouse located at 450 Golden Gate Avenue, San Francisco, California 94102, Defendants Global Blood Therapeutics, Inc. and Pfizer Inc. ("Defendants") will and hereby do move the Court for an order dismissing Plaintiffs' First Amended Complaint pursuant to Rules 12(b)(1), 12(b)(6), and 9(b) of the Federal Rules of Civil Procedure.

This Motion is made on the following grounds:

1. Plaintiffs' state-law claims (Counts 1, 2, 4–13) are preempted by federal law;
2. Plaintiffs fail to plead their fraud-based claims (Counts 4, 6–10, 12, 13) with particularity as required by Rule 9(b), and therefore fail to state claims upon which relief can be granted under Rule 12(b)(6);
3. Plaintiffs lack Article III standing to assert claims on behalf of a nationwide class (Counts 1, 2, 4, 5);
4. Plaintiffs lack Article III standing to pursue claims for injunctive relief (Counts 5, 6, 10, 12, 13);
5. The First Amended Complaint fails to state a claim upon which relief may be granted for a violation of the Magnuson-Moss Warranty Act (Count 3);
6. The First Amended Complaint fails to state claims upon which relief may be granted for violations of state consumer protection statutes (Counts 7–10) that contain safe-harbor provisions exempting federally-regulated conduct from their reach; and
7. Plaintiffs fail to plausibly allege that they are entitled to punitive damages.

Defendants respectfully request an order dismissing with prejudice all causes of action brought against them in the above-captioned matter. This Motion is based upon this Notice of Motion and Motion to Dismiss; the attached Memorandum of Points and Authorities; the accompanying Request for Judicial Notice and Declaration of Teresa M. Wogoman; any reply memorandum; the pleadings and files in this action; and such other matters Defendants may present at or before the hearing.

Dated: April 23, 2025

Respectfully submitted,

By: /s/ *Jessica Bodger Rydstrom*

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MEMORANDUM OF POINTS AND AUTHORITIES

I. INTRODUCTION

Plaintiffs Rickey Jolly, Amanda Winbush, Antonio Johnson, Kristy Keyes, Courtney McDaniel, Ekuwo Ngongo, and Jermaine Harshaw are former purchasers of Oxbryta (voxelotor), a prescription medication approved by the FDA for the treatment of sickle cell disease ("SCD"). In this putative consumer class action, Plaintiffs contend that Oxbryta was "worth nothing" when they paid for it because recent clinical data suggested an "imbalance" in vaso-occlusive crises and fatal events in certain patients taking the medication. Notably, Plaintiffs do ***not*** allege that they suffered any adverse physical effects from Oxbryta. Instead, they seek monetary damages to reimburse them for some unspecified amount of "out-of-pocket costs" incurred in "acquiring Oxbryta"—alleging wide-ranging claims of fraud and breach of warranties against Defendants Global Blood Therapeutics, Inc. ("GBT") and Pfizer Inc. After Defendants moved to dismiss the Original Complaint, Plaintiffs filed their First Amended Complaint ("Amended Complaint" or "FAC"). Even as amended, Plaintiffs' claims fail as a matter of law and should be dismissed.

Plaintiffs' amended state-law claims (Counts 1, 2, 4–13)—all of which are premised on a failure-to-warn theory—fail to surmount the threshold problem identified by Defendants in their earlier motion to dismiss: these claims are preempted by federal law. Under Supreme Court precedent, state-law failure-to-warn claims are preempted unless the defendant can unilaterally change the drug's label under an FDA regulation called "Changes Being Effected" ("CBE"). Unlike their Original Complaint, the Amended Complaint acknowledges this regulation—but it still fails to offer facts demonstrating that the CBE regulation would have applied here, which is necessary to avoid preemption. On this basis alone, all of Plaintiffs' state-law claims premised on a failure-to-warn theory should be dismissed.

In addition to being preempted, Plaintiffs' state-law claims fail for multiple other reasons. Plaintiffs assert claims for common law fraud (Count 4) and violations of state consumer protection statutes (Counts 6–10, 12, 13). All of those claims "sound in fraud," and so must be stated with particularity under Rule 9(b). But, even as amended, Plainitffs' conclusory statements about Defendants' efforts to "actively conceal[]" information about Oxbryta or

"intentionally . . . mislead" consumers fall far short of this standard, and must be dismissed. Plaintiffs also seek to represent a nationwide class in connection with their claims for breach of express and implied warranties (Counts 1, 2), unjust enrichment (Count 5), and common law fraud (Count 4). As representatives of only seven states, they lack standing to do so. Similarly, Plaintiffs fail to demonstrate that they have standing to pursue the injunctive relief they seek in connection with their claims under Georgia, Florida, and Louisiana law (Counts 6, 10, 11) because they do not plead that they are likely to suffer an "imminent" injury from future purchases of Oxbryta.

Plaintiffs' sole federal claim, for a violation of the Magnuson-Moss Warranty Act ("MMWA") (Count 3), also fails. To begin, Oxbryta is not a "consumer product" within the meaning of the MMWA, which precludes any individual or class-wide claims based on this statute. Separately, Plaintiffs plainly do not meet the 100-named-plaintiff requirement to bring a class action under the MMWA, nor do they allege adequate pre-suit notice. For all these reasons, the Amended Complaint should be dismissed.

II. BACKGROUND

This case is about Oxbryta (voxelotor), a prescription medicine developed by GBT for the treatment of sickle cell disease. SCD is a rare inherited blood disorder affecting approximately 100,000 people in the United States. FAC ¶ 41. It is caused by a gene mutation that affects hemoglobin, the protein in red blood cells that is responsible for delivering oxygen throughout the body. *Id.* ¶¶ 43, 45. In patients with SCD, abnormal hemoglobin causes red blood cells to become rigid, sticky, and "sickle"-shaped; these sickled red blood cells clump together and restrict the flow of oxygen, causing pain events called vaso-occlusive crises ("VOCs"), acute chest syndrome, swelling, anemia, and strokes—among other complications. *Id.* ¶ 44.

In November 2019, the FDA granted Oxbryta accelerated approval for use by adults and pediatric patients aged 12 years and older, and, in December 2021, expanded the medication's approved use to patients as young as 4 years old. *Id.* ¶ 49. The FDA's accelerated approval program expedites review of medications designed to address unmet medical needs in the treatment of serious or life-threatening conditions. *See* 21 C.F.R. § 314.500. Eligible medications can obtain accelerated approval "on the basis of adequate and well-controlled clinical trials establishing that

the drug product has an effect on a surrogate endpoint" that is reasonably likely "to predict clinical benefit." *Id.* § 314.510. The FDA's approval of Oxbryta was based on (among other data) the results of the HOPE clinical trial, a randomized, double-blind, placebo-controlled, multi-center clinical trial that demonstrated an improvement in hemoglobin response (the FDA-sanctioned endpoint "reasonably likely to predict clinical benefit"). *See* Wogoman Decl. Ex. 1 at 4, 12 (FDA, Summary Review for Regulatory Action).[1] As it does for all medicines in the accelerated approval program, the FDA required GBT to conduct post-marketing studies demonstrating Oxbryta's clinical benefits and assessing its long-term safety. *See* Wogoman Decl. Ex. 2 at 2–5 (FDA Approval Letter).

Sponsors of medications that are granted accelerated approval must submit their proposed labeling to the FDA, following specific regulatory requirements. 21 C.F.R. § 201.56(a)(1). The label for a drug granted accelerated approval must also "acknowledge that [it] was approved based upon accelerated approval and that continued approval for the drug (or indication) may be contingent upon verification and description of clinical benefit in a confirmatory trial or trials." *See* Wogoman Decl. Ex. 4 at 3 (FDA, Labeling Under Accelerated Approval Guidance (Jan. 2019)). Oxbryta's FDA-approved label included information about the HOPE trial, and disclosed that the drug's indication was "approved under accelerated approval based on increase in hemoglobin."[2] *See* Wogoman Decl. Ex. 3 at 1 (Oxbryta Label).

After Pfizer acquired GBT in October 2022, it continued to study the benefits and safety of Oxbryta. In September 2024, Pfizer announced the voluntary withdrawal of Oxbryta following an initial review of available data from new clinical studies and patient registry-based studies, which

[1] The Court may take judicial notice of documents posted to the FDA's public website without converting a motion to dismiss into one for summary judgment. *See Gustavson v. Wrigley Sales Co.*, 961 F. Supp. 2d 1100, 1113 n.1 (N.D. Cal. 2013).

[2] Sponsors of medications that are granted accelerated approval must submit to the FDA "copies of all promotional materials, including promotional labeling as well as advertisements" within 120 days after approval. 21 C.F.R. § 314.550. Even after that initial 120-day time period, the sponsor is required to submit any "promotional material" or labeling at least 30 days prior to the dissemination of the labeling or initial publication of the advertisement. *Id.*

appeared to show an imbalance in VOCs in certain patients and a small number of fatal events which required further assessment. *See* FAC ¶ 65.

Shortly thereafter, on December 23, 2024, four named plaintiffs filed this putative class action. *See* Compl., ECF No. 1. Defendants moved to dismiss the Original Complaint on February 26, 2025. *See* Defs.' Mot. to Dismiss, ECF No. 21. Plaintiffs filed their Amended Complaint on April 2, 2025. *See* FAC, ECF No. 38.

The seven Plaintiffs named in the Amended Complaint are residents of Indiana, Virginia, Georgia, Florida, Louisiana, North Carolina, and Pennsylvania.[3] All Plaintiffs allege that a "healthcare provider[]" prescribed Oxbryta to them, and that Plaintiffs "paid out of pocket for Oxbryta." FAC ¶¶ 12, 14, 16, 18–21. Notably, ***none*** of the Plaintiffs allege that he or she suffered ***any*** adverse effect from the medication. *See id.* ¶ 110 (excluding "claims for personal injury or wrongful death"). Instead, Plaintiffs contend that Oxbryta was "worth nothing," and they "would not have bought [Oxbryta]" had they known about "the true risks" of the medication. *Id.* ¶¶ 103(f), 137, 180. Plaintiffs assert claims of breach of express and implied warranties (Counts 1, 2), violation of the MMWA (Count 3), common law fraud (Count 4), unjust enrichment (Count 5), redhibition under Louisiana law (Count 11), and violations of Indiana, Virginia, Georgia, Florida, North Carolina, and Pennsylvania consumer protection statutes (Counts 6–10, 12–13).[4] In addition to their individual claims, Plaintiffs seek to represent a nationwide class and seven state subclasses

[3] The Original Complaint was filed on behalf of four named plaintiffs, one of whom (Darryl Weekly) is no longer a party to the Amended Complaint.

[4] Plaintiff Johnson brings claims alleging violations of the Georgia Uniform Deceptive Trade Practices Act ("GUDTPA"), Ga. Code. Ann. § 10-1-370 *et seq.* (Count 6) and the Georgia Fair Business Practices Act ("GFBPA"), Ga. Code. Ann. § 10-1-390 *et seq.* (Count 7). Plaintiff Jolly brings a claim alleging violations of the Indiana Deceptive Consumer Sales Act ("IDCSA"), Ind. Code § 24-5-0.5-1 *et seq.* (Count 8). Plaintiff Winbush brings a claim alleging violations of the Virginia Consumer Protection Act ("VCPA"), Va. Code Ann. § 59.1–196 *et seq.* (Count 9). Plaintiff Keyes brings a claim alleging violations of the Florida Deceptive and Unfair Trade Practices Act ("FDUTPA"), Fla. Stat. § 501.201 *et seq.* (Count 10). Plaintiff McDaniel brings a redhibition claim under Louisiana law, La. Civ. Code art. 2520 *et seq.* (Count 11). Plaintiff Ngongo brings a claim alleging violations of the North Carolina Unfair and Deceptive Trade Practices Act ("NCUDTPA"), N.C. Gen Stat. § 75–1 *et seq.* (Count 12). Plaintiff Harshaw brings a claim alleging violations of the Pennsylvania Unfair Trade Practices and Consumer Protection Law ("UTPCPL"), 73 Pa. Cons. Stat. § 201-1 *et seq.* (Count 13).

of purchasers who paid at least some portion of Oxbryta "out-of-pocket" from November 1, 2019 to the present. *Id.* ¶ 109.

III. ISSUES TO BE DECIDED

1. Are Plaintiffs' state-law claims preempted by federal law?

2. Do Plaintiffs fail to plead their fraud-based claims with particularity as required by Rule 9(b)?

3. Do Plaintiffs lack Article III standing to assert claims on behalf of a nationwide class?

4. Do Plaintiffs lack Article III standing to seek injunctive relief?

5. Do Plaintiffs fail to state a claim for violation of the MMWA?

6. Are Plaintiffs' claims under under the Georgia, Indiana, Virginia, and Florida consumer protection statutes barred by those statutes' safe harbor provisions?

7. Do Plaintiffs fail to plausibly plead that they are entitled to punitive damages?

IV. LEGAL STANDARD

A. Federal Rule of Civil Procedure 12(b)(1).

A complaint must be dismissed if the court lacks subject matter jurisdiction. Fed. R. Civ. P. 12(b)(1). "[T]he plaintiff bears the burden of establishing subject matter jurisdiction." *Abbasfar v. Chertoff*, 2007 WL 2409538, at *2 (N.D. Cal. Aug. 21, 2007). "A court must presume lack of jurisdiction until the plaintiff establishes otherwise." *Id.* If a plaintiff lacks standing, then the Court lacks subject matter jurisdiction. *Pirozzi v. Apple Inc.*, 913 F. Supp. 2d 840, 846 (N.D. Cal. 2012).

B. Federal Rule of Civil Procedure 12(b)(6).

To avoid dismissal under Rule 12(b)(6), a complaint must "contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (quoting *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007)). The Court need not "accept as true allegations that are merely conclusory, unwarranted deductions of fact, or unreasonable inferences." *Sprewell v. Golden State Warriors*, 266 F.3d 979, 988 (9th Cir. 2001).

C. Federal Rule of Civil Procedure 9(b).

Claims sounding in fraud must be stated with "particularity." Fed. R. Civ. P. 9(b). To satisfy this requirement, plaintiffs must "identify 'the who, what, when, where, and how of the misconduct charged,' as well as 'what is false or misleading about [the purportedly fraudulent conduct], and why it is false." *Cafasso, ex rel. United States v. Gen. Dynamics C4 Sys., Inc.*, 637 F.3d 1047, 1055 (9th Cir. 2011) (citation omitted). "[M]ere conclusory allegations of fraud are insufficient." *Moore v. Kayport Package Express, Inc.*, 885 F.2d 531, 540 (9th Cir. 1989).

V. ARGUMENT

A. Plaintiffs' State-Law Claims Are Preempted (Counts 1, 2, 4–13).

The Supremacy Clause provides that "the Laws of the United States . . . shall be the supreme Law of the Land." U.S. Const. art. VI, cl. 2. State laws "that conflict[] with federal law" are thus "without effect." *Cipollone v. Liggett Grp., Inc.*, 505 U.S. 504, 516 (1992) (citation omitted). There are two types of preemption: express and implied. Implied preemption occurs when "state and federal law conflict" such that it is "impossible for a private party to comply with both state and federal requirements." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011) (citation omitted). As to pharmaceutical products, implied conflict preemption bars state-law claims "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency." *Id.* at 623–24. That doctrine applies here, requiring dismissal of Plaintiffs' state-law claims—***all*** of which are premised on a theory that Defendants failed to warn "Oxbryta users" of "the risk of increased VOCs, infections, stroke, and/or death." *See, e.g.*, FAC ¶¶ 9, 124(b), 131.

"[F]ederal law expressly forbids a manufacturer from changing its label after the label has received FDA approval unless such changes are made pursuant to the CBE regulation." *Utts v. Bristol-Myers Squibb Co.*, 226 F. Supp. 3d 166, 184–85 (S.D.N.Y. 2016). Accordingly, to avoid dismissal on preemption grounds, Plaintiffs "must allege facts showing that [defendants] could have unilaterally changed [the drug's] label under the CBE regulation." *Mahnke v. Bayer Corp.*, 2019 WL 8621437, at *3 (C.D. Cal. Dec. 19, 2019) (citation omitted). The CBE regulation permits

a manufacturer to unilaterally change an approved drug's label only if there is (1) "newly acquired information," 21 C.F.R. § 314.70(c)(6)(iii), that shows (2) "more than an indeterminate or inconclusive relationship" between the drug and a clinically significant risk, *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1175 (S.D. Cal. 2016); *see also Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 305 (2019). Plaintiffs attempt to invoke this regulation by citing medical publications, reports of adverse events, the pause of a clinical trial, and "interim results of ongoing clinical and registry studies." FAC ¶ 85. For the reasons below, none of this information satisfies the CBE prerequisites, and so Plaintiffs' failure-to-warn claims are preempted.

Plaintiffs first contend that there was "newly-acquired, mounting evidence" that the "use of Oxbryta would result in a net decrease of oxygen delivery," and a corresponding increase in VOCs. *Id.* ¶ 59. But Plaintiffs undermine their own claim that information about Oxbryta's oxygen delivery was "newly acquired" by citing to an article dated 2017 (two years before the FDA's approval) and by alleging that "[c]oncern" about oxygen delivery has been "voiced repeatedly in the medical literature" since that date. *Id.* Plaintiffs do not plead any facts—beyond mere speculation—that this "medical literature" was not considered by the FDA. *Id.* The Amended Complaint also cites articles assessing the results of the HOPE study, claiming the results of that trial confirm "voxelotor's adverse effect on oxygen delivery." *Id.* ¶¶ 57, 58. But the FDA assessed the risk of voxelotor's ability to deliver oxygen, considering "concern[s]" that the medication's "offloading of O2 from voxelotor-bound [hemoglobin] in the tissues could be decreased."[5] The Complaint does not identify what "risks of a different type or greater severity" were established in the articles cited to satisfy the definition of "newly acquired information." 21 C.F.R. § 314.3.

Plaintiffs next point to adverse event reports made to the FDA's Adverse Event Reporting System ("FAERS") as evidence of "newly acquired" information about which Defendants should have warned Oxbryta users. *See* FAC ¶ 80. FDA regulations require pharmaceutical companies to submits reports for "[a]ny adverse event associated with the use of a drug in humans, ***whether or not considered drug related***." 21 C.F.R. § 314.80(a) (emphasis added). The regulations also

[5] *See* Wogoman Decl. Ex. 5, NDA Review § 8.2.5.1 ("Effect of Voxelotor on Tissue Oxygen Availability").

"disclaim any implication of causation as to the FAERS data." *Pietrantoni v. Concept Therapeutics Inc.*, 640 F. Supp. 3d 197, 206 n.3 (D. Mass. 2022) (citing 21 C.F.R. § 314.80(l)). The fact that "a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event." *Gayle v. Pfizer Inc.*, 452 F. Supp. 3d 78, 88 (S.D.N.Y. 2020), *aff'd*, 847 F. App'x 79 (quoting *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011)). Accordingly, courts consistently hold that these reported events do not meet the CBE regulation's definition of "newly acquired information." *See Bueno v. Merck & Co., Inc.*, 2024 WL 3974754, at *14 (S.D. Cal. Aug. 27, 2024) ("adverse events" in "FDA database" are not "newly acquired evidence"); *Gayle*, 452 F. Supp. 3d at 88 (holding that "6,000 adverse event reports relating to diabetes sent from Pfizer to the FDA" do not constitute "newly acquired information" because they do not indicate causal association); *Ignacuinos v. Boehringer Ingelheim Pharms., Inc*., 490 F. Supp. 3d 533, 543 (D. Conn. 2020) (holding that adverse event reports are not "newly acquired information" unless they "provide reasonable evidence of a causal association"); *McGrath v. Bayer Healthcare Pharms., Inc.*, 393 F. Supp. 3d 161, 169 (E.D.N.Y. 2019) (holding that "[r]eports and studies that discuss the *fact* of" adverse events but do not indicate a causal connection are not "newly acquired information"); *Pietrantoni*, 640 F. Supp. 3d at 214 (holding that FAERS reports "fail to establish the existence of 'newly acquired information'"). Nothing in the Amended Complaint warrants a different result here.

Plaintiffs also claim that Defendants failed to warn Plaintiffs that they "paused dosing in two global clinical studies . . . as of May 2024 due to safety concerns." FAC ¶ 68. But they fail to allege facts demonstrating that a potential safety concern in a clinical trial was sufficient to invoke the CBE regulation, which requires information demonstrating "more than an indeterminate or inconclusive relationship" between the drug and a clinically significant risk. *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1175 (S.D. Cal. 2016). Plaintiffs themselves cite to an EMA Report that indicates the data available at the time needed "further review[]" to determine "whether there is an impact on the benefit-risk balance of Oxbryta." *See* FAC ¶ 68 n.30.[6] The

[6] *See* European Medicines Agency, Assessment Report on Temporary Measures, Procedure under Article 20 of Regulation (EC) No 726/2004, Oxbryta EMEA/H/A-20/1538/C/004869/0014 (Sept.

Complaint fails to allege facts showing how this statement satisfies the requirements of the CBE regulation.

Finally, Plaintiffs claim that Defendants failed to warn about the imbalance of VOCs suggested in "interim results" from Defendants' clinical trials and real-world registry studies. *Id.* ¶ 85. But this theory has a timing problem. The Amended Complaint cites statements from regulators in September 2024, indicating that available clinical data suggest an "increase in VOCs" in patients taking Oxbryta. *See, e.g.*, FAC ¶ 77. That, of course, is when Defendants voluntarily withdrew Oxbryta from the market, citing the need to further investigate available data regarding study participants taking voxelotor. *Id.* ¶ 5. The Amended Complaint does not allege facts demonstrating that any "newly acquired" analysis of this data was available to Defendants with sufficient time to initiate a label change before the product was withdrawn from the market. *See In re Chantix (Varenicline) Mktg., Sales Pracs. & Prods. Liab. Litig. (No. II)*, 735 F. Supp. 3d 352, 388 (S.D.N.Y. 2024) (dismissing failure-to-warn claim where "Plaintiffs fail[ed] to plausibly allege that Defendant was in possession of that newly acquired information at any point prior to its decision to recall [the drug]" and observing that the defendant "opt[ed] to address the issue with a recall, rather than an application pursuant to the CBE process").

Having failed to allege "newly acquired" information that would permit a unilateral modification to Oxbryta's label under the CBE regulation, the Amended Complaint faults Defendants for failing to "adequately test" for "adverse effects," FAC ¶ 82, and claims they "downplayed" risks associated with Oxbryta, *id.* ¶ 53. Neither theory salvages Plaintiffs' preempted failure-to-warn claims. "[A]sserting that a manufacturer could or should have done more studies—i.e., that a manufacturer should have created the newly acquired information—is insufficient to avoid preemption under the CBE regulation." *Holley v. Gilead Scis., Inc.*, 2023 WL 6390598, at *8 (N.D. Cal. Sept. 28, 2023) (internal quotation marks omitted) (citing *Gayle*, 452 F. Supp. 3d at 88). Likewise, allegations that Defendants misled the FDA by withholding information are themselves preempted by the FDCA. *See Buckman Co. v. Pls.' Legal Comm.*, 531 U.S. 341,

26, 2024), https://www.ema.europa.eu/en/documents/referral/oxbryta-article-20-procedure-assessment-report-temporary-measures_en.pdf.

350 (2001). Plaintiffs' state-law claims premised on failure-to-warn allegations should be dismissed.

B. Plaintiffs' Fraud-Based Claims Should be Dismissed (Counts 4, 6–10, 12, 13).

Even if Plaintiffs' state-law claims could survive preemption, their fraud-based claims must be dismissed under Rules 9(b) and 12(b)(6). The Amended Complaint asserts a "common law fraud" claim (Count 4) as well as claims under Indiana, Virginia, Georgia, Florida, North Carolina, and Pennsylvania consumer fraud statutes (Counts 6–10, 12, 13). Underlying ***all*** of these claims are allegations that Defendants engaged in "fraudulent" or "deceptive" conduct by making intentional and material "misrepresentations" about the safety of Oxbryta and "omitt[ing]" or "actively conceal[ing]" information about alleged risks.[7] Because all of these claims are "grounded in fraud," they must be pled with particularity under Rule 9(b). *Vess v. Ciba-Geigy Corp. USA*, 317 F.3d 1097, 1103–04 (9th Cir. 2003); *see also Kearns v. Ford Motor Co.*, 567 F.3d 1120, 1125 (9th Cir. 2009) (a claim can be "grounded in fraud" or "sound in fraud" even if fraud is not a necessary element of the claim). Defendants raised this same argument in support of their motion to dismiss the Original Complaint. *See* Defs.' Mot. to Dismiss at 7–10, ECF No. 21. In response, Plaintiffs have merely added more conclusory, boilerplate statements devoid of the factual content necessary to satisfy Rule 9(b)'s heightened pleading standard, and so Plaintiffs' fraud-based claims should be dismissed with prejudice.

1. Plaintiffs Fail to Plausibly Allege Any Affirmative Misrepresentation.

Plaintiffs first allege that Defendants "affirmatively misrepresented" material facts about the "safety" or "benefits" of Oxbryta. *See, e.g.*, FAC ¶¶ 8, 103(c), 103(e), 103(f), 229, 244. But the ***only*** specific information each Plaintiff claims that he or she relied on in deciding to purchase Oxbryta was the "product packaging," which included the (FDA-required) statement that the medication was "indicated for the treatment of sickle cell disease."[8] FAC ¶¶ 12, 14, 16, 18–21,

[7] *See, e.g.*, FAC ¶¶ 8, 191–197, 213–220, 226–233, 241–248, 250, 257–263, 269–273, 302–308, 315–322.

[8] Plaintiffs also claim to have relied on the "Pfizer brand name," FAC ¶¶ 12, 14, 16, 18–21, but that is not an actionable "statement" to support a fraud claim. And, as a practical matter, Pfizer did not

125. This allegation cannot support a plausible claim for a "misrepresentation"; any information included on the labeling of an FDA-approved drug is directed by strict regulations and reflects FDA's determination that the information is not "false or misleading." 21 C.F.R. § 314.125(b)(6).

Although the Amended Complaint provides additional examples of Defendants' advertisements and promotional materials, Plaintiffs still fail to identify which, if any, of these statements they ***actually saw or relied on*** in deciding to purchase Oxbryta. *See Kearns*, 567 F.3d at 1126 (affirming dismissal where plaintiff "failed to specify which sales material he relied upon in making his decision to buy" the product); *Tabler v. Panera LLC*, 2019 WL 5579529, at *12 (N.D. Cal. Oct. 29, 2019) ("[C]ourts in this circuit have held that a plaintiff does not satisfy Rule 9(b) when the plaintiff generally identifies allegedly misleading statements but fails to specify which statements the plaintiff actually saw and relied upon.").

Finally, Plaintiffs fail to allege the "particular circumstances" surrounding any alleged misrepresentation. *Kearns*, 567 F.3d at 1126; *Azar v. Gateway Genomics, LLC*, 2017 WL 1479184, at *7 (S.D. Cal. Apr. 25, 2017) (requiring plaintiffs to allege the "who, what, when, where, and how" of the fraud). For example, Plaintiffs fail to allege "when" they saw ads or labels, "where" they saw them, and "under what circumstances." *Id.*; *see also In re Volkswagen "Clean Diesel" Mktg., Sales Pracs., & Prods. Liab. Litig.*, 349 F. Supp. 3d 881, 914 (N.D. Cal. 2018) (holding that the plaintiff failed to satisfy Rule 9(b) where the complaint failed to identify "where she saw this advertising," as well as "what type of advertising it was"); *In re NJOY, Inc. Consumer Class Action Litig.*, 2014 WL 12586074, at *10–11 (C.D. Cal. Oct. 20, 2014) (same). The failure to include these facts warrants dismissal of Plaintiffs' "misrepresentation" claims under Rule 9(b).

2. Plaintiffs Fail to Allege "Active Concealment" With Particularity.

Plaintiffs also allege that Defendants "actively concealed" facts about Oxbryta's safety. *See, e.g.*, FAC ¶¶ 103, 105, 218, 231, 246, 261, 306, 320. To state a claim for "active concealment," Plaintiffs must point to "specific affirmative acts" Defendants took "in hiding, concealing or

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acquire GBT until October 2022, and so the notion that Plaintiffs have been relying on the Pfizer "brand" since 2019 is literally impossible.

covering up the matters complained of." *Herron v. Best Buy Co.*, 924 F. Supp. 2d 1161, 1176 (E.D. Cal. 2013) (citation and quotation marks omitted). Plaintiffs' repeated "generalized allegations" that Defendants "actively concealed" information about Oxbryta's purported safety risks fall far short of this standard. *Id.* There are ***zero*** factual allegations of any "affirmative acts" taken by Defendants to "conceal" information about Oxbryta. Accordingly, Plaintiffs should not be permitted to proceed with their "active concealment" theory of fraud.

3. Plaintiffs Fail to Allege an Actionable Omission.

Plaintiffs' fraud-by-omission theory also fails. To state an omission-based claim, Plaintiffs must allege facts indicating that Defendants "knew" of the "risk of increased VOCs" ***at the time Plaintiffs filled their prescriptions.*** *Ahern v. Apple Inc.*, 411 F. Supp. 3d 541, 564–66 (N.D. Cal. 2019) (citation omitted) ("[A] defendant 'must have known of the defect at the time of sale for a plaintiff to state a claim for fraud by omission.'"); *Victorino v. FCA US LLC*, 2018 WL 1083395, at *8 (S.D. Cal. Feb. 27, 2018) ("When addressing a defendant's pre-sale knowledge, courts have held that the defendant must have knowledge of the specific defect alleged[.]"). Although the Complaint repeatedly asserts that Defendants "knew or should have known" about "the risk of increased VOCs," these threadbare legal conclusions merely recite the elements of Plaintiffs' fraud claim or the language of the relevant consumer protection statutes.[9] The Complaint lacks facts demonstrating that Defendants were "aware" of a "risk of increased VOCs" when Plaintiffs purchased Oxbryta at some unspecified time "within the last four years." FAC ¶¶ 12–21. Absent "sufficient factual matter" to "make th[e] inference plausible" that Defendants "knew" about an alleged "defect" when Plaintiffs filled their prescriptions, Plaintiffs' omission-based claims fail. *In re Nexus 6P Prods. Liab. Litig.*, 293 F. Supp. 3d 888, 908 (N.D. Cal. 2018); *see also Azar*, 2017 WL 1479184, at *5 (dismissing fraud claims due to threadbare conclusions of knowledge); *Mandani v. Volkswagen*, 2019 WL 652867, at *7–8 (N.D. Cal. Feb. 15, 2019) (same).

Plaintiffs cannot salvage their fraud-by-omission claims by alleging that Defendants were "in a superior position to know" of Oxbryta's potential risks. FAC ¶¶ 102, 190. These "generalized

[9] *See, e.g.*, FAC ¶¶ 6, 9, 186, 187, 213, 226, 241, 257, 302, 315.

allegations" of "exclusive" or superior knowledge are insufficient to defeat a dismissal motion. *Hovsepian v. Apple, Inc.*, 2009 WL 5069144, at *3 (N.D. Cal. Dec. 17, 2009); *Andren v. Alere, Inc.*, 207 F. Supp. 3d 1133, 1142 (S.D. Cal. 2016).

C. Plaintiffs Lack Article III Standing For a Nationwide Class or Injunctive Relief.

At an "irreducible constitutional minimum," Article III of the Constitution requires Plaintiffs to plead that they have personally suffered some actual or threatened injury due to Defendants' conduct and that the injury is "fairly traceable to the challenged action" and is "likely . . . [to be] redressed by a favorable decision." *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560–61 (1992) (cleaned up). Plaintiffs do not have standing to: (a) assert claims under laws of states where Plaintiffs themselves did not purchase Oxbryta; or (b) pursue injunctive relief in connection with any of their claims.

1. Plaintiffs Lack Standing to Assert Nationwide Class Claims (Counts 1, 2, 4, 5).

Plaintiffs, who are residents of only seven states, lack standing to pursue state-law claims on behalf of a nationwide class of consumers. *Biederman v. FCA US LLC*, 2025 WL 458831, at *4 (N.D. Cal. Feb. 11, 2025). "[D]istrict courts in this Circuit routinely hold plaintiffs do not have standing to pursue class claims under the common laws of states to which the named plaintiffs have no connection[.]" *Id.* (cleaned up). Where, as here, a "representative plaintiff is lacking for a particular state, all claims based on that state's laws are subject to dismissal." *Pardini v. Unilever United States Inc.*, 961 F. Supp. 2d 1048, 1061 (N.D. Cal. 2013).[10] Plaintiffs can seek only to represent putative class members consisting of their own states' residents.

Moreover, Plaintiffs' claims for breach of express and implied warranties (Counts 1, 2), unjust enrichment (Count 5), and common law fraud (Count 4)—all pleaded on behalf of a

[10] In *Melendres v. Arpaio*, the Ninth Circuit framed this issue as one of "class certification" as opposed to "standing." 784 F.3d 1254, 1262 (9th Cir. 2015). But courts in this jurisdiction have subsequently dismissed claims brought on behalf of a nationwide class prior to class certification where, as here, "plaintiffs brought claims under the laws of multiple states where they did not reside and where they were not injured." *Jones v. Micron Tech. Inc.*, 400 F. Supp. 3d 897, 909, 911 (N.D.

"[n]ationwide class"—should be dismissed because Plaintiffs have failed to allege ***which state's*** law governs them.[11] "[C]ourts in this district have held that, due to variances among state laws, failure to allege which state law governs a common law claim is grounds for dismissal."[12] *Sidhu*, 2022 WL 17170159, at *3 (citation omitted); *see also In re Nexus*, 293 F. Supp. 3d at 933 (citation omitted) ("As this Court and other courts in this district have recognized, 'due to variances among state laws, failure to allege which state law governs a common law claim is grounds for dismissal.'"). Because Plaintiffs assert their common law claims on behalf of a nationwide class without alleging which state law governs, those claims should be dismissed.

2. Plaintiffs Lack Standing to Pursue Injunctive Relief (Counts 6, 10, 11).

Plaintiffs' requests for injunctive relief fare no better. There are no factual allegations in the Amended Complaint demonstrating that Plaintiffs face a "real and immediate threat" of harm from future purchases of Oxbryta—nor could there be at present, given that the medicine was voluntarily withdrawn from the market in September 2024. *City of Los Angeles v. Lyons*, 461 U.S. 95, 105 (1982); *see Gatling-Lee v. Del Monte Foods, Inc.*, 2023 WL 11113888, at *5 (N.D. Cal. Mar. 28, 2023) (concluding that "Plaintiffs lack standing to seek injunctive relief" because they could not plausibly allege they would purchase the product in the future). Moreover, Plaintiffs' own allegation that Oxbryta was "worth nothing" when they purchased it, FAC ¶ 180, undermines any plausible claim of future harm. *See Min Sook Shin v. Umeken USA, Inc.*, 773 F. App'x 373, 375 (9th Cir. 2019).

Cal. 2019) ("*Melendres* does not, in the Court's view, stand for the proposition that this Court must delay its consideration of standing in sister state cases until class certification.").

[11] Plaintiffs request that the Court construe their "unjust enrichment" claim as one in "quasi-contract" under California law, FAC at 44 n.51, but they never actually contend that California law applies to this claim.

[12] Although some courts in this jurisdiction have considered the failure to identify which state law governs as a "pleading problem," *see Ablaza v. Sanofi-Aventis U.S. LLC*, 2023 WL 2942983, at *4 (N.D. Cal. Apr. 13, 2023), others have addressed it as part of the standing analysis, *Sidhu v. Bayer Healthcare Pharms. Inc.*, 2022 WL 17170159, at *2–3 (N.D. Cal. Nov. 22, 2022) (dismissing common law claims asserted "on behalf of a nationwide class"). Under either analysis, the Amended Complaint here is inadequate.

Injunctive relief is the only remedy available for Plaintiffs' claim under the GUDTPA (Count 6). *See Willingham v. Glob. Payments, Inc.*, 2013 WL 440702, at *16 (N.D. Ga. Feb. 5, 2013) ("Injunctive relief is the sole remedy under the [G]UDTPA."). Given that Plaintiffs lack standing to pursue injunctive relief—the sole form of relief available under the GUDTPA—Count 6 should be dismissed in its entirety. Similarly, Plaintiffs cannot pursue injunctive relief in connection with their claims under the FDUTPA (Count 10) or Louisiana redhibition law (Count 11). *See, e.g.*, FAC ¶¶ 282, 296.

D. Plaintiffs' Magnuson-Moss Warranty Act Claim Fails (Count 3).

Plaintiffs' MMWA claim fails for three independent reasons.[13] ***First***, the Amended Complaint fails to state a claim under the MMWA—on an individual or class-wide basis—because Oxbryta is not a "consumer product" within the meaning of that statute. 15 U.S.C. § 2301. As the Amended Complaint acknowledges, Oxbryta is a "prescription medication," FAC ¶ 1, and so is regulated by the FDCA, 21 U.S.C. § 321(g)(1). A drug regulated by the FDCA is "not a consumer product within the meaning of Magnuson-Moss." *Kanter v. Warner-Lambert Co.*, 99 Cal. App. 4th 780, 798 (2002). As a result, "[w]here the FDCA governs the product at issue, a plaintiff may not state a claim under the MMWA." *Mollicone v. Universal Handicraft, Inc.*, 2017 WL 440257, at *12 (C.D. Cal. Jan. 30, 2017).

Second, under the MMWA, "[n]o claim shall be cognizable . . . if the action is brought as a class action, and the number of named plaintiffs is less than one hundred." 15 U.S.C. § 2310(d)(3)(C). Plaintiffs assert their MMWA claim on behalf of a putative class, but the Amended Complaint names only seven plaintiffs—93 short of the MMWA's requirement. On that basis, Plaintiffs' MMWA claim should be dismissed.[14] *See Patterson v. RW Direct, Inc.*, 2018 WL

[13] If the Court dismisses Plaintiffs' breach of express and implied warranty claims (Counts 1, 2), then the MMWA claim also fails. *Clemens v. DaimlerChrysler Corp.*, 534 F.3d 1017, 1022 (9th Cir. 2008) (MMWA claims "stand or fall with . . . express and implied warranty claims.").

[14] Plaintiffs cannot rely on the Class Action Fairness Act ("CAFA") to evade the MMWA's 100-plaintiff requirement. *See Floyd v. Am. Honda Motor Co., Inc.*, 966 F.3d 1027, 1034–35 (9th Cir. 2020) (holding that "a requirement for an MMWA class action in federal court is at least one hundred named plaintiffs" and "CAFA may not be used to evade or override the MMWA's specific numerosity requirement").

6106379, at *2 (N.D. Cal. Nov. 21, 2018) (dismissing with prejudice MMWA claim asserted by only one named plaintiff on behalf of a putative class).

Third, Plaintiffs do not allege that they provided adequate pre-suit notice to proceed with their MMWA claim as a class action. The MMWA requires a named plaintiff to notify the defendant they are acting on behalf of the class and afford the defendants a "reasonable opportunity" to cure any failure to comply with the statute. *See* 15 U.S.C. § 2310(e); *Stearns v. Select Comfort Retail Corp.*, 763 F. Supp. 2d 1128, 1143 (N.D. Cal. 2010). The Amended Complaint does not satisfy either requirement. Instead, Plaintiffs allege that they "need not have given" pre-suit notice for the MMWA claim because they "may give such notice . . . after class certification pursuant to 15 U.S.C. § 2310(e)." FAC ¶ 183. Not so. "[T]he argument that a class action plaintiff need not provide pre-suit notice is wholly without support." *Morrison v. Ross Stores, Inc.*, 2018 WL 5982006, at *5 (N.D. Cal. Nov. 14, 2018). Plaintiffs' failure to allege that they satisfied the requirements of § 2310(e) warrants dismissal of their MMWA claim with prejudice. *Nadler v. Nature's Way Prods., LLC*, 2014 WL 12601567, at *3–4 (C.D. Cal. Mar. 27, 2014).

E. Plaintiffs' Claims Under Georgia, Indiana, Virginia, and Florida Consumer Protection Statutes Are Barred by Those Statutes' Safe Harbor Provisions (Counts 7–10).

Plaintiffs' claims under the Georgia, Indiana, Virginia, and Florida consumer protection statutes identified in Counts 7–10 should be dismissed because each statute contains a safe harbor provision explicitly excluding federally-regulated conduct from its reach. *See* Ga. Code. Ann. § 10-1-396 (GFBPA does not apply to "actions or transactions specifically authorized under laws administered by or rules and regulations promulgated" by a federal agency.);[15] Ind. Code § 24-5-0.5-6 (IDCSA "does not apply to an act or practice that is . . . expressly permitted by federal law, rule, or regulation."); Va. Code Ann. § 59.1–199 (VCPA does not apply to "[a]ny aspect of a

[15] Separately, Plaintiff Johnson cannot pursue a claim under the GFBPA on behalf of "the Georgia Subclass" because an action under that statute cannot be brought "in a representative capacity." Ga. Code Ann. § 10-1-399(a); *see also Corcoran v. CVS Health Corp.*, 169 F. Supp. 3d 970, 993 (N.D. Cal. 2016) (dismissing GFBPA claim because "[t]he GFBPA indisputably forecloses claims brought 'in a representative capacity'").

consumer transaction" that is "authorized under laws or regulations" of the United States.); Fla. Stat. § 501.212(1) (FDUTPA "does not apply to . . . [a]n act or practice required or specifically permitted by federal or state law.").

Plaintiffs allege that Defendants violated these state statutes by "misrepresenting" information about Oxbryta's "characteristics" and "benefits." FAC ¶¶ 229, 244, 259, 272. These claims go to the heart of activities regulated by the FDA. Any statements about Oxbryta included in the product's advertisements and labeling are subject to strict FDA regulations. *See, e.g.*, 21 C.F.R. §§ 201.56, 202.1(e)(4)(i)(a), 314.50(e), 314.70(b)(2)(v), 314.550. Plaintiffs have not offered sufficient facts to demonstrate that Defendants could have unilaterally altered those statements without the FDA's prior approval. *See supra* Section A. Accordingly, Plaintiffs' claims under these state consumer protection statutes are not actionable because they fall squarely within the relevant safe harbor provisions. *See, e.g.*, *Ball v. Takeda Pharms. Am., Inc.*, 963 F. Supp. 2d 497, 500 (E.D. Va. 2013) (concluding that state consumer protection statutes do not apply to "transactions in federally-regulated prescription drugs"); *Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228, 1234 (S.D. Fla. 2007) (dismissing claims regarding advertisements "implicitly authorized" by the FDA based on FDUTPA safe harbor provision and substantially similar Massachusetts provision).

F. The Court Should Dismiss or Strike Plaintiffs' Request for Punitive Damages.

Although Plaintiffs request "punitive damages," they fail to plead that they are entitled to such relief. A plaintiff seeking punitive damages "must identify actual facts, as opposed to conclusory allegations showing that the defendant acted [with oppression, fraud or malice]." *Gutierrez v. Kaiser Permanente*, 2018 WL 2412319, at *5 (E.D. Cal. May 29, 2018) (dismissing complaint with boilerplate punitive allegations). In addition, to plausibly plead punitive damages against a corporation, Plaintiffs must allege facts to show that an officer, director, or managing agent acted with oppression, fraud or malice. *See Funke v. Sorin Group, USA, Inc.*, 147 F. Supp. 3d 1017, 1028 n.2 (C.D. Cal. 2015). The Amended Complaint fails both requirements. For the reasons explained *supra* Section B, Plaintiffs have failed to plead facts establishing that Defendants

acted with "fraud." They also make no attempt to plead "oppression, fraud or malice" on the part of any officer, director, or managing agent of these corporate defendants. Plaintiffs cannot pursue punitive damages based on these deficient allegations.

VI. CONCLUSION

For the foregoing reasons, Defendants respectfully request that the Court dismiss the Amended Complaint in its entirety, with prejudice.

Dated: April 23, 2025

Respectfully submitted,

By: */s/ Jessica Bodger Rydstrom*

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CERTIFICATE OF SERVICE

I certify that on April 23, 2025, I electronically filed the foregoing Motion to Dismiss with the Clerk of Court using the ECF system, which sent notification of such filing to all counsel of record.

/s/ *Jessica Bodger Rydstrom*
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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

RICKEY JOLLY, *et al.*, individually and on behalf of others similarly situated,

Plaintiffs,

v.

GLOBAL BLOOD THERAPEUTICS, INC. and PFIZER INC.,

Defendants.

Case No. 3:24-cv-09345-TLT

REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS THE FIRST AMENDED COMPLAINT

Date: July 8, 2025
Time: 2:00 PM
Location: Courtroom 9 – 19th Floor
Judge: Hon. Trina L. Thompson

Pursuant to Federal Rule of Evidence 201(b), Defendants Global Blood Therapeutics, Inc. and Pfizer Inc. ("Defendants") request that the Court take judicial notice of the following documents cited in the Memorandum of Points and Authorities in support of their Motion to Dismiss the First Amended Complaint. Defendants' request is supported by the Declaration of Teresa M. Wogoman ("Wogoman Declaration") filed herewith.

1. FDA Center for Drug Evaluation & Research, Division Director Summary Review for Regulatory Action (Nov. 25, 2019), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf ("Summary Review for Regulatory Action"), attached as **Exhibit 1** to the Wogoman Declaration.

2. FDA Approval Letter for Oxbryta (NDA 213137) (Nov. 25, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/213137Orig1s000ltr.pdf ("Approval Letter"), attached as **Exhibit 2** to the Wogoman Declaration.

3. Oxbryta Label (Nov. 2019) approved by FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213137s000lbl.pdf ("Oxbryta Label"), attached as **Exhibit 3** to the Wogoman Declaration.

4. FDA, Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry (Jan. 2019), https://www.fda.gov/media/119755/download ("Labeling Under Accelerated Approval Guidance"), attached as **Exhibit 4** to the Wogoman Declaration.

5. Excerpts of FDA, NDA Multi-Disciplinary Review and Evaluation (Nov. 24, 2019), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf ("NDA Review"), attached as **Exhibit 5** to the Wogoman Declaration.

Judicial Notice. Courts can take judicial notice of facts "capable of accurate and ready determination by resort to sources whose accuracy cannot be reasonably questioned." Fed. R. Evid. 201(b). Documents published to the FDA's public website are proper subjects of judicial notice. *See Gustavson v. Wrigley Sales Co.*, 961 F. Supp. 2d 1100, 1113 n.1 (N.D. Cal. 2013) (taking judicial notice of FDA documents on motion to dismiss and stating that "[t]he Court may take judicial notice of materials available on government agency websites"); *Eidmann v. Walgreen Co.*,

522 F. Supp. 3d 634, 642 (N.D. Cal. 2021) ("Documents published on government-run websites are proper for judicial notice."). By "tak[ing] judicial notice of 'matters of public record,'" a court does not "convert[] a motion to dismiss into a motion for summary judgment." *Lee v. City of Los Angeles*, 250 F.3d 668, 689 (9th Cir. 2001). Judicial notice of the Summary Review for Regulatory Action (**Ex. 1**), Approval Letter (**Ex. 2**), Oxbryta Label (**Ex. 3**), Labeling Under Accelerated Approval Guidance (**Ex. 4**), and NDA Review (**Ex. 5**) is proper because these documents are matters of public record available on the FDA's public website and are thus "not subject to reasonable dispute." Fed. R. Evid. 201(b); *see Gustavson*, 961 F. Supp. 2d at 1113 n.1; *Eidmann*, 522 F. Supp. 3d at 642.

Dated: April 23, 2025

Respectfully submitted,

By: */s/ Jessica Bodger Rydstrom*

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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

RICKEY JOLLY, *et al.*, individually and on behalf of others similarly situated,

Plaintiffs,

v.

GLOBAL BLOOD THERAPEUTICS, INC. and PFIZER INC.,

Defendants.

Case No. 3:24-cv-09345-TLT

DECLARATION OF TERESA M. WOGOMAN IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS THE FIRST AMENDED COMPLAINT

Date: July 8, 2025
Time: 2:00 PM
Location: Courtroom 9 – 19th Floor
Judge: Hon. Trina L. Thompson

I, Teresa M. Wogoman, hereby declare as follows:

1. I am an associate at the law firm of Williams & Connolly LLP, counsel of record for Defendants Global Blood Therapeutics, Inc. and Pfizer Inc. ("Defendants") in this action. I am admitted *pro hac vice* to appear before this Court in the above-captioned action.

2. I submit this declaration in support of Defendants' Motion to Dismiss the First Amended Complaint and the accompanying Request for Judicial Notice. All facts set forth below are personally known to me and are true and correct, and I would testify to them under penalty of perjury if called as a witness.

3. Attached as **Exhibit 1** is a true and correct copy of the document titled "Division Director Summary Review for Regulatory Action" published by the U.S. Food and Drug Administration ("FDA") and dated November 25, 2019. This document is publicly available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf. At my direction, a copy of this document was accessed and printed on April 22, 2025.

4. Attached as **Exhibit 2** is a true and correct copy of the FDA Approval Letter for Oxbryta (NDA 213137) dated November 25, 2019. This document is publicly available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/213137Orig1s000ltr.pdf. At my direction, a copy of this document was accessed and printed on April 22, 2025.

5. Attached as **Exhibit 3** is a true and correct copy of the FDA-approved label for Oxbryta dated November 2019. This document is publicly available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213137s000lbl.pdf. At my direction, a copy of this document was accessed and printed on April 22, 2025.

6. Attached as **Exhibit 4** is a true and correct copy of the document titled "Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry," published by the FDA and dated January 2019. This document is publicly available at https://www.fda.gov/media/119755/download. At my direction, a copy of this document was accessed and printed on April 22, 2025.

7. Attached as **Exhibit 5** is a true and correct copy of excerpts of the document titled "NDA Multi-Disciplinary Review and Evaluation" published by the FDA and dated November 24,

2019. The complete document (comprising more than 200 pages) is publicly available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf. At my direction, a copy of this document was accessed, printed, and excerpted on April 22, 2025.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that this declaration was executed this 23rd day of April 2025 in Arlington, VA.

Teresa M Wogoman

Teresa M. Wogoman

EXHIBIT 1

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA #213137
Applicant	Global Blood Therapeutics
Date of Submission	06/26/2019
PDUFA Goal Date	2/26/2020
Proprietary Name	Oxbryta
Established or Proper Name	Voxelotor (GBT440)
Dosage Form(s)	500 mg tablet
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of sickle cell disease in adult (b) (4) patients.
Action or Recommended Action:	*Accelerated Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older. This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) (1).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	**Katie Chon, PharmD, RPh**
Medical Officer Review	**Patricia Oneal, MD/Rosanna Setse, MD PhD**
Statistical Review	**Lola Luo, PhD/ Yeh-Fong Chen, PhD**
Pharmacology Toxicology Review	**Pedro L. Del Valle, PhD/Brenda J. Gehrke, PhD/ Haleh Saber, PhD, MS**
OPQ Review	**Gaetan Ladoucer/Su Tran/Nina Ni/Anamitro Banerjee/Abdullah Mahmud/Sherita McLamore, PhD/Mei Ou, PhD; Banu Zolnik, PhD; Angelica Dorantes, PhD; Rabiya Haider, PharmD;James Laurensen**
Microbiology Review	**N/A**
Clinical Pharmacology Review	**Salaheldin Hamed, PhD, Jianghong Fan, PhD, Liang Li, PhD, Robert Schuck, PharmD, PhD/Christian Grimstein, PhD, Lian Ma, PhD Xinyuan Zhang, PhD, Ruby Leong, PharmD/ Brian P Booth, PhD**
OPDP	**Rob Nguyen, PharmD**
OSI	**Anthony Orencia, MD; Min Lu, MD, MPH,**

	Kassa Ayalew, MD, MPH
CDTL Review	**Tanya Wroblewski, MD**
OSE/DEPI	**Richard Swain MD; Kate Gelperin MD**
OSE/DMEPA	**Stephanie DeGraw, PharmD; Hina Mehta, PharmD**
OSE/DRISK	**Mei-Yean Chen; Naomi Boston**
Labeling	**Virginia Kwitkowski**
Others	**Please see unireview**

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Benefit-Risk

Sickle cell disease (SCD) is a serious and life-threatening inherited chronic disorder affecting approximately 100,000 Americans and millions world-wide. The disease is caused by a mutation in the beta-globin gene resulting in the polymerization of deoxygenated HbS and resultant sickling of red blood cells (RBCs). SCD is characterized clinically by hemolytic anemia and recurrent painful vasoocclusive crisis (VOC), acute chest syndrome (ACS), priapism as well as progressive multiple end-organ damage including stroke/silent cerebral infarct, chronic kidney disease, leg ulcers, pulmonary hypertension and sickle cell anemia-associated nephropathy (SCAN). Patients with SCD can have significant morbidity as well as a shortened lifespan. The hemoglobin level in patients with SCD is one measure that reflects the severity and clinical course of the disease. Patients with lower hemoglobin levels tend to have an increased risk for end-organ complications such as chronic kidney disease, pulmonary hypertension, stroke and silent cerebral infarctions and early mortality. Treatment includes symptom improvement, antibiotic prophylaxis, strategies to increase the fetal hemoglobin, and reduce the number of vasooclusive crises. For a few patients, hematopoietic stem cell transplantation can be quite effective.

Despite the availability of hydroxyurea, L-glutamine, and crizanlizumab, all of which have been demonstrated effectiveness in reducing the number of vasoocclusive pain or acute chest syndrome episodes, a significant need still exists for effective treatments. Interventions that may reduce hemolysis resulting in an increase in blood hemoglobin (Hgb) levels may confer a clinical benefit in this patient population.

Global Blood Therapeutics has developed a hemoglobin S polymerization inhibitor for daily oral use for use in patients with SCD. The pivotal study, GBT440-031, demonstrated a statistically significant improvement in the number of patients treated with 1500 mg voxelotor compared to the number of patients treated with placebo who had a one gram per deciliter of hemoglobin rise in their hemoglobin levels from baseline at Week 24 (51.2% vs 6.2%, respectively). Additionally, there was a dose dependent reduction in hemolysis markers (bilirubin and percent reticulocytes). The most common treatment emergent adverse events were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia. Serious adverse reactions included headache, drug hypersensitivity and pulmonary embolism. Labeling addresses the safety concerns and includes warnings for hypersensitivity reactions and potential laboratory interference as voxelotor administration may interfere with measurement of Hb subtypes (HbA, HbS, and HbF) by high performance liquid chromatography (HPLC).

Potential theoretical risks with voxelotor include tissue hypoxia due to ineffective tissue oxygen extraction with the high Hgb occupancy from voxelotor-bound hemoglobin. This theoretical risk of tissue hypoxia could lead to end-organ dysfunction. Overall, no clinical safety concerns with inadequate tissue oxygenation

were identified in the voxelotor program to date. The long-term safety of voxelotor will be assessed with post-marketing requirements and commitments.

In summary, the overall safety profile of voxelotor appears acceptable for proposed registrational dose of 1,500 mg and current data support a favorable benefit-risk assessment for voxelotor for patients with sickle cell disease. The labeling adequately addresses known risks and the Applicant intends to confirm and verify clinical benefit with an ongoing confirmatory study.

Rationale for Accelerated Approval

Section 21 CFR 314.500 provides that the FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval under these regulations requires that the applicant study the product further to verify and describe the clinical benefit. The regulation states that the expectation that the verification study would usually be underway at the time of the approval and that the confirmatory study be adequate and well-controlled.

As noted above, the Applicant has demonstrated the effect of voxelotor on an endpoint that is reasonably likely to predict clinical benefit in adults and pediatric patients with sickle cell disease age 12 years and older. The hemoglobin improvement was due to a reduction in hemolysis. While the increase in hemoglobin results represent substantial evidence of an effect, it is not entirely clear that an increase of a gram per deciliter or more of hemoglobin due to voxelotor results in a tangible benefit to patients. For that reason, this application is receiving accelerated approval with a post-marketing requirement to provide evidence of clinical benefit. During negotiations with the Applicant several proposals for demonstrating clinical benefit were discussed. At this time, the Applicant has chosen to demonstrate that an improvement in hemoglobin due to voxelotor is associated with a reduction in cerebral blood flow velocity as assessed by transcranial doppler (TCD) velocity.

Background for the accelerated approval

A major benefit in the treatment of sickle cell disease would be to demonstrate a decrease in the risk of strokes for patients with sickle cell disease.

An NHLBI analysis of patients with SCD identified two phenotypes: those who had complications (stroke, renal failure, pulmonary hypertension, priapism, leg ulcers, early mortality) that appeared to be associated with a “hyper-hemolytic phenotype” and those who had complications that appeared to be associated with vasooclusive events.

Patients with sickle cell disease experience significant morbidity due to the risk of strokes including silent strokes. A recent analysis suggests that patients with lower hemoglobin levels tend to have an increased risk for end-organ complications such as

chronic kidney disease, pulmonary hypertension, stroke and silent cerebral infarctions and early mortality. TCD is used to assess cerebral artery blood flow velocity and is a reliable predictor of stroke.

Several important trials have been conducted to understand hemoglobin levels and stroke or silent cerebral infarct risk in patients with sickle cell. Two clinical trials have established that routine TCD screening and chronic red cell transfusions for children with abnormal TCD as the standard of care for stroke prevention: The Stroke Prevention Trial in Sickle Cell Anemia (STOP) and Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2). STOP was a randomized multicenter controlled trial comparing prophylactic blood transfusion with standard care in children aged 2 to 16 years with SCD selected for high stroke risk by TCD. The study showed a reduction in stroke with transfusion. In STOP2, discontinuing transfusions after 30 months or more resulted in a reversion to abnormal TCD values and increased stroke risk. The Silent Cerebral Infract Transfusion (SIT) trial randomized patients to chronic blood transfusion or observation and followed them with magnetic resonance imaging (MRI). The patients who received chronic transfusions had fewer recurrences of infarct or hemorrhage. The chronic transfusions that patients with SCD receive are not risk free and can lead to alloantibody formation, iron overload and risks of infections.

TCD readings are usually reported as normal, conditional, and abnormal or inadequate for assessment. Based on the trials mentioned above a chronic transfusion program is recommended for patients with high risk TCD measurements (abnormal category) to reduce stroke risk. The risk of stroke based on TCD measurement is thought to be a continuous variable and not a discrete one. Therefore, patients with conditional TCD results may still be at risk for stroke albeit less than those patients with abnormal TCD results.

The Applicant has proposed a controlled study (STUDY GBT440-032) to confirm the clinical benefit of voxelotor by evaluating the effect of voxelotor on stroke risk reduction as measured by TCD flow velocity in patients with sickle cell anemia and will include patients aged < 12 years as the confirmatory trial under subpart H.

1. Background

The following text is excerpted from the draft unireview:

Sickle-cell disease (SCD) is a life-threatening, hereditary, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States (Yawn, Buchanan et al. 2014). A single point mutation in the hemoglobin β-globin chain of affected persons produces mutant hemoglobin molecules (Hemoglobin S [Hb S]). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States. Approximately 25% of patients have coinheritance of Hb

S with another β-globin chain variant such as sickle-Hb C disease and sickle β-thalassemia.

During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting in intermittent vaso-occlusive events and chronic hemolytic anemia. Vaso-occlusion occurs as a result of the formation of multicellular aggregates that block blood flow in small blood vessels, resulting in tissue ischemia & reperfusion damage to downstream tissues which lead to recurrent acute pain/crises episodes. Vaso-occlusive pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (Platt, Thorington et al. 1991, Gill, Sleeper et al. 1995). The cumulative effect of recurrent vasoocclusive episodes and sustained hemolytic anemia result in multiple end-organ complications including diastolic heart disease, pulmonary hypertension, splenic dysfunction; hepatobiliary disease and chronic kidney disease.

SCD is associated with decreased life expectancy (Platt 1994, Lanzkron, Carroll et al. 2013, Elmariah, Garrett et al. 2014, Maitra, Caughey et al. 2017). Acute chest syndrome (ACS) is a serious acute complication and a leading cause of mortality in both children and adults with SCD (Vichinsky, Neumayr et al. 2000, Bakanay, Dainer et al. 2005). Other causes of death in patients with SCD include infections (Adamkiewicz, Sarnaik et al. 2003) and cerebrovascular events (Platt 2005, Verduzco and Nathan 2009).

Children have higher rates of death from infection and sequestration crises (Manci, Culberson et al. 2003). Cardiopulmonary complications represent a major mortality risk in adults (Fitzhugh, Lauder et al. 2010). Currently, the management of sickle cell crises (SCC) episodes is generally supportive and includes symptomatic treatment with intravenous fluids, analgesics, oxygen and RBC transfusion support. Hematopoietic stem cell transplantation (HSCT) and gene therapy offers potential cure; however only few patients are eligible for these treatment option. Hydroxyurea (HU) was approved in 1998 and 2017; for reducing the frequency of sickle cell crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months) and for reducing the frequency of painful crises and the need for blood transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises. L-glutamine (approved in 2017) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

Recently Novartis received approval for a monoclonal antibody targeting selectin to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

Global Blood Therapeutics has submitted an NDA for GBT440 (Voxelotor (OXBRYTA)), a new molecular entity, which is not currently marketed anywhere in the world. GBT440 binds to the N-terminal α chain of Hb, increases HbS affinity for

oxygen, delays in vitro HbS polymerization and prevents sickling of red blood cells (RBCs).

2. Product Quality

From the Office of Product Quality Summary review:

NDA 213137 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act for Voxelotor Tablets, 500 mg. Voxelotor is a once daily, orally bioavailable, small-molecule, hemoglobin S polymerization inhibitor …Voxelotor is a new molecular entity (NME) that was granted Fast Track designation (October 2015); Orphan Designation (December 2015); Rare Pediatric Disease Designation (Jun 2017); and Breakthrough Therapy Designation (January 2018)… Voxelotor is a small, achiral, BCS Class 2 molecule, that is manufacturedcby (b) (4) *. The drug product is presented as 500 mg immediate-release solid oral dosage form and is formulated as a light yellow to yellow, biconvex, oval-shaped, film-coated, tablet with "GBT 500" debossed on one side.*

Voxelotor is to be administered alone or in combination with hydroxyurea. The recommended dosing regimen for Voxelotor Tablets is 1500 mg taken orally once daily with or without food and 1000 mg taken orally once daily in patients with severe hepatic impairment (Child Pugh C)…

The applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The key review issues (Section IV) have been adequately resolved and were deemed to have minimal likely impact on patient efficacy or safety and do not preclude approval of this product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, Oxbryta (Voxelotor) Tablets possess the necessary attributes to ensure that the product meets the quality target product profile (b) (4)

3. Nonclinical Pharmacology/Toxicology

From the executive summary portion of the nonclinical review (unireview):

Evidence from X-ray crystallography studies show that voxelotor binds covalently and reversibly via a Schiff-base to the N-terminal valine of one hemoglobin α-chain to stabilize the oxyHb state. Voxelotor increases O2 affinity with a half maximal EC50 of approximately 21 μM in a dose-dependent manner. Because the binding of voxelotor is distant from the heme pockets, voxelotor increases O2 affinity without sterically blocking the release of O2. Approximately 90% of voxelotor partitions into RBC when added to human whole blood favored by its higher affinity (10-fold) for Hb over albumin indicating that less compound remains in the plasma compartment upon oral dosing to humans. Voxelotor bound to Hb maintains and stabilizes oxyHb under hypoxic conditions that delays the transition from oxyHb to deoxygenated Hb

(deoxyHb) and favors the delay in polymerization as well. Results of ex vivo studies provided evidence that voxelotor may delay in vivo HbS polymerization in patients with SCD and causes a corresponding dose-dependent decrease in the number of sickled RBC (SSRBC) under hypoxic conditions. Voxelotor was also shown to reduce the viscosity of SS blood and improves deformability of SSRBC under hypoxic conditions in ex-vivo studies using blood samples from patients with SCD. Blood samples of Townes sickle cell mice treated with voxelotor showed an increase in Hb-O2 affinity and anti-sickling activity with a significant reduction in the number of ex vivo SSRBC.

In secondary pharmacology screens, voxelotor had activity in micromolar ranges, producing >50% inhibition against the dopamine transporter, the GABA receptor complex, the angiotensin receptor 1, the phosphodiesterase 4A1A enzyme, and the insulin receptor. The safety pharmacology evaluation of voxelotor included a panel of in vitro and in vivo studies. No voxelotor-related effects occurred in the neurological evaluations in rats or in the in vitro assessments on the hERG potassium current. In a cardiovascular study in dogs, voxelotor produced higher (↑8%) mean systolic pressure at 1000 mg/kg at 6 hours post-dose. In an assessment of respiratory function in rats, voxelotor produced lower tidal volume (↓13%) at 1000 mg/kg and increased respiration rate (↑19%) at 320 and 1000 mg/kg; no voxelotor-related effects on respiratory function occurred at the low dose of 100 mg/kg.

The pharmacokinetics of voxelotor was characterized in multiple species, including mice, rats, dogs and monkeys. The time to maximal blood concentration (tmax) of voxelotor following oral administration was approximately 0.6 to 8 hours. Voxelotor oral bioavailability ranged from 36% to 71% and was limited by both absorption in the gut and first-pass metabolism in the liver. Terminal elimination half-life was similar between whole blood and plasma for each species tested and ranged from approximately 6 hours in mouse plasma to 94 hours in dogs. Blood:plasma concentration ratios ranged from 69 to 74, consistent with the preferential binding to Hb and partition into RBC. Voxelotor binds to plasma proteins (99%) across all animal species tested and human. In general, voxelotor displayed less than dose-proportional increases in exposure in all species with limited or no increase above 250 mg/kg in the rat, 300 mg/kg in the dog, and 300 mg/kg in the monkey. Voxelotor showed lower exposures in pregnant rats and rabbits compared to non-pregnant animals, and there were no differences in exposure between sexes. Distribution trends of radiolabeled [14C]-voxelotor in the nonpigmented rats were generally comparable to those seen in pigmented male rats with the highest peak concentrations in blood, lung, spleen, liver, bone marrow and kidney. Elimination of labeled voxelotor from tissues was nearly complete by 168 hours postdose and not detectable by 672 hours postdose.

Voxelotor was extensively metabolized by oxidation-reduction and conjugation reactions in in vitro metabolism studies using human liver microsomes and recombinant enzymes and in vivo in rat and dog (approximately 85% of the dose

administered). Rats excreted approximately 15-16% and dogs excreted < 1% of the administered dose unchanged in feces and urine, respectively. The majority of metabolites generated in humans were also present in the mouse, rat and dog. The major circulating metabolite in human plasma accounting for 16.8% of the total radioactivity was M218/1, an O-dealkylated voxelotor metabolite that is conjugated with sulfate. This conjugated metabolite does not partition into RBC and it is not expected to be pharmacologically active. Further results of voxelotor metabolism in vitro and in vivo conditions are discussed in the Clinical Pharmacology section.

Repeat-dose toxicology studies of up to 26-week in rats and 39-week in monkeys were conducted. In the rat study, voxelotor was administered at 0, 15, 50, or 250 mg/kg/day. Findings of increased erythroid and myeloid parameters (red blood cell mass, reticulocytes and WBC), increases in spleen and thymus organ weights, microscopic findings of hypercellularity in the bone marrow, and extramedullary hematopoiesis and changes in lymphocytes in the spleen occurred mostly at the mid-dose (MD) and high dose (HD). These findings may be associated with a physiological response to the pharmacological action of voxelotor of increased oxygen affinity of hemoglobin. Additional findings included increases in liver weight that corresponded with microscopic findings of periportal hepatocyte hypertrophy and bile duct hyperplasia, and thyroid follicular hypertrophy and pituitary basophil hypertrophy that may be associated with the induction of hepatic metabolizing enzymes. Lower glucose, cholesterol and triglycerides concentrations may be associated with effects on body weight. There were signs of inflammation in several organs at the HD including the harderian gland, kidney, lung, nonglandular stomach, prostate, rectum and thymus that were not present at recovery except for the nonglandular stomach. Urine volume increases at the MD and HD corresponded with diuresis and microscopic findings of chronic progressive nephropathy that was not present at recovery. Most findings were not present at recovery except for the hyperplasia/hyperkeratosis in the stomach and chronic active inflammation in the nonglandular stomach.

In the 39-week monkey study, voxelotor was administered at 0, 15, 30, or 60 mg/kg/day. Mortality occurred at MD and HD with adverse clinical signs, macroscopic findings in the GI tract and skin and adverse microscopic findings in lymphatic organs, GI tract and kidney. Increases in red blood cells at all doses, increases in reticulocytes at the HD, increases in hematocrit, and increases in spleen weight with corresponding increases in red pulp cellularity occurred in male monkeys. Increases in red blood cells, hemoglobin, hematocrit and reticulocytes were present in the HD at recovery. Decreased mean corpuscular volume of ≤10% occurred at all dose levels in males and females and were still present in the HD at the end of recovery. Decreases in white blood cells were present only in males at the HD but values rebounded at the end of recovery. Voxelotor produced a general decrease in all immunophenotype cell subsets that was transient and not dose-dependent. A delayed/transient suppressed

immune response across dose levels was observed. Relevant microscopic findings that suggest an inflammatory response in the heart, liver, lungs and spleen, mostly at the MD and HD, were still present at recovery.

Voxelotor was not mutagenic in a bacterial reverse mutation (Ames) assay, or clastogenic in an in vivo micronucleus test in rats. Voxelotor was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model.

Developmental and reproductive toxicology studies conducted with voxelotor included: fertility and early embryonic development (FEED) in rats, embryo fetal development (EFD) in rats and rabbits, and pre- and postnatal development (PPND) in rats. In the FEED study in rats, voxelotor was administered at doses of 0, 15, 50, or 250 mg/kg/day following the standard ICH S5(R2) design. Relevant findings in HD animals included higher testis and prostate weights, lower seminal vesicle with fluid weight and adverse findings in sperm motility and morphology, compared to control. Despite those findings, there were no functional effects on male or female fertility. No voxelotor effects occurred in EFD studies in rats at doses of 0, 15, 50, or 250 mg/kg/day and in rabbits at doses of 0, 25, 75 or 150 mg/kg/day. In the PPND study in rats, voxelotor was administered at doses of 0, 15, 50 or 250 mg/kg/day during gestation day (GD) 6 through Lactation Day 20. Voxelotor-related effects in F0 dams at the HD included lower body weight gain during gestation, lower food consumption during gestation and lactation, and increased mean postimplantation loss. Effects in offspring at the maternal HD included lower Day 4 viability index, and adverse lower body weight of pups during Lactation Day 0-21. An increased number of stillborn pups occurred at all doses but was not dose-dependent. Voxelotor-related effects in F1 offspring included lower body weights through the maturation phase to Post-Pairing Day 55 (males) and Maturation Day 7 (females). Effects on the reproductive performance in F1 males included lower fecundity and fertility indexes in MD and HD, and in F1 females, lower fertility index, lower number of corpora lutea, lower number of implantations and lower number of live fetuses also in the MD and HD.

*The adopted pharmacologic class for voxelotor is a hemoglobin S polymerization inhibitor. Because voxelotor preferentially partition into RBC, all comparisons in animal and human exposure defined in the label were based on assessments in whole blood. The AUC for human exposure in whole blood used for this purpose was 3820 µg/mL*h.*

There are no outstanding issues from a nonclinical perspective that would prevent approval of voxelotor for the treatment of sickle cell disease in adult (b) (4) *patients.*

4. Clinical Pharmacology

From the executive summary of the Clinical Pharmacology Section of the unireview:

Exposure-efficacy analyses identified a positive and a statistically significant relationship between voxelotor exposure in whole blood and hemoglobin response (change from baseline, CFB). Exposure-safety analyses identified a positive relationship between Grade ≥ 1 ALT elevation and voxelotor plasma exposure; additionally, a relationship was identified for decreased white blood cell count (WBC) and diarrhea. Collectively, exposure-response analyses supported the proposed 1500 mg dose.
The key review questions focused on dose recommendations for patients with severe hepatic impairment, exposure in HbSC genotype, and drug-drug interactions based on coadministration of CYP3A4 modulators.
In subjects with severe hepatic impairment, voxelotor whole blood and plasma AUC increased by 90% compared to subjects with normal hepatic function. A dose reduction to 1000 mg daily is recommended in patients with severe hepatic impairment.

Patients with the HbSC genotype had a 50% higher whole blood AUC and 45% higher Cmax compared to HbSS or HbSβ0 at steady-state. No dose adjustment is recommended for patients with HbSC genotype.

CYP3A4 exhibits the most significant contribution to the metabolism of voxelotor (36% to 56%). A PBPK model based on detailed in vitro metabolism and ADME studies was utilized to predict the effect of CYP3A4 modulation on the PK of voxelotor. Concomitant administration of drugs that are strong CYP3A4 inhibitors is predicted to increase voxelotor by 40% to 80%. Concomitant administration of fluconazole (a moderate CYP3A/CYP2C9 and strong CYP2C19 inhibitor) is predicted to increase voxelotor by 73% to 100%; of note, fluconazole inhibits other enzymes that play a marginal role in the metabolism of voxelotor. Concomitant administration of strong CYP3A4 inhibitors or fluconazole should be avoided. If unavoidable, a dose reduction to 1000 mg daily is recommended for patients receiving concomitant medications that are strong inhibitors of CYP3A4 or fluconazole.
Concomitant medications that are strong or moderate inducers of CYP3A4 are predicted to decrease voxelotor exposure by 50 to 73%. Concomitant administration of strong or moderate CYP3A4 inducers should be avoided. If unavoidable, the recommended dose for patients receiving concomitant strong or moderate inducers of CYP3A4 is 2500 mg daily.

Recommendations

The proposed dosing regimen of 1500 mg once daily in adult (b) (4) *patients with sickle cell disease is acceptable. From a clinical pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language. There are no postmarketing requirements or commitments.*

5. *Clinical* Microbiology – N/A

6. Clinical/Statistical-Efficacy

GBT conducted a randomized, double-blind, placebo-controlled, multi-center trial (HOPE). The Hope trial enrolled 274 patients randomized based on hydroxyurea usage and geographic region and age to receive 1500 mg daily (n=90), 900 mg daily (n=92), or placebo (n=92). Approximately 65% of patients were on stable doses of hydroxyurea. Approximately 67% of enrolled patients were African-American with almost 22% were Arab/Middle Eastern. Most patients had the SCD genotype SS. The enrolled population reflects those with the condition. Efficacy was based on Hb response rate defined as the proportion of patients with Hb increase of greater than or equal to 1 g/dL at Week 24. Approximately 23% of all enrolled patients discontinued early from the study. The most common reason was withdrawal of consent. The response rate for voxelotor 1500 mg was 51.1% (46/90) and 900 mg was 32.6% (30/92) compared to 6.5% (6/92) in the placebo group ($p < 0.0001$). Trial results also demonstrated dose dependent improvements in bilirubin and percent reticulocytes. There was a trend for an improvement in LDH but it was not statistically significant. There was no difference in annualized vasoocclusive events across the three arms and specifically, no increase in the voxelotor treatment arms. An unusual finding concerning leg ulcers was seen in the trial. Although the incidence of leg ulcers was low, in the 1500 mg group all 4 patients with leg ulcers improved whereas no patients with leg ulcers improved in the placebo group and two patients developed them. In the 900 mg group the results were mixed with some patients having an improvement and some patients having no change, and at least one patient who developed a leg ulcer.

The HOPE trial was supported by multiple other studies including Bioequivalence and Bioavailability studies, Pharmacokinetic, and Initial Tolerability Studies, Drug-Drug Interaction Studies, Food Effect, Exercise Physiology, Controlled and Uncontrolled Clinical Studies in healthy subjects, patients with SCD and patients with idiopathic pulmonary fibrosis.

7. Safety

GBT submitted data came from 22 trials in healthy volunteers, patients with SCD, and patients with idiopathic pulmonary fibrosis. Approximately 280 patients with SCD were exposed to at least one dose of voxelotor including 29 pediatric patients. Most of the safety data came from the HOPE trial where patients had the longest exposure to treatment. The Applicant also enrolled a few patients on an expanded access program.

In the pivotal HOPE trial, the most common treatment emergent adverse events were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia. Serious adverse reactions considered related to voxelotor treatment were headache, drug hypersensitivity and pulmonary embolism (reported in no more than 1 subject each).

The two major issues for labeling were 1) hypersensitivity reactions of which a grade 3 was reported in one patient who had positive rechallenges and 2) reported laboratory test interference when using chromatography to document hemoglobinopathy result. Otherwise most of the adverse events were headache, pyrexia, gastrointestinal (diarrhea, abdominal pain, nausea) rash or fatigue.

Specifically, not seen with this application were TQT prolongation and liver injury or any significant changes to other laboratory parameters (other than those reported in section 6 above).

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee meeting as there were no major concerns regarding the safety or efficacy findings from the trials.

9. Pediatrics

Pediatric patients from less than 17 to 12 were eligible to enroll in the clinical trials. The HOPE trial enrolled 29 pediatric patients of which 14 received the 1500 mg daily dose. Efficacy, safety and pharmacokinetics were similar to those seen with adult patients.

The required confirmatory PMR trial under accelerated approval will study younger pediatric patients and more efficacy and safety data will be obtained.

10. Other Relevant Regulatory Issues

No outstanding regulatory issues were uncovered during the review process including:

- Application Integrity Policy (AIP)- none
- Exclusivity or patent issues of concern - none
- Office of Scientific Investigations (OSI) Audits did not uncover any issues during inspection.
- Financial Disclosure - none

- Other Good Clinical Practice (GCP) issues - none

11. Labeling

The labeling adequately reflects the data GBT submitted with respect to the discipline reviews. The HOPE trial results are in sections 6 and 14 of the labeling. Two Warnings are placed in the labeling: hypersensitivity and laboratory test interference.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

A REMS plan was not necessary for product approval.

- Other Postmarketing Requirements and Commitments

PMR-1 (Accelerated Approval PMR)

Complete Study GBT440-032: the ongoing Phase 3, randomized, double-blind, placebo-controlled trial in pediatric patients (age 2 years to < 15 years) with Sickle Cell Disease (HOPE Kids 2). Expected enrollment of approximately 224 patients (age 2 years to < 15 years) with at least 15 patients from age 2 years to < 4 years of age. Include patients with baseline hemoglobin of less than 6 g/dL. The primary endpoint is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by transcranial doppler (TCD). The secondary endpoint is change from baseline in TCD flow velocity at Week 48 and Week 96.

Interim Report Submission
(based on primary analysis): 07/2025
Study/Trial Completion: 03/2026
Final Report Submission: 09/2026

PMR-2 (Accelerated Approval PMR)

Complete follow-up of patients (on treatment) enrolled in Study GBT440-031: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease (HOPE Trial).
Conduct an updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Study/Trial Completion: 12/2019
Final Report Submission: 09/2020

PMC

Complete at least 5 years of follow-up for all patients (on treatment) enrolled in Study GBT440-034: An Open-Label Extension Study of voxelotor Administered Orally to Patients with Sickle Cell Disease who have Participated in GBT440 Clinical trials. Include updated safety and efficacy analysis in yearly reports and submit datasets at the time of final clinical study report submission.

Interim Report Submission (Year 1):	06/2021
Interim Report Submission (Year 2):	06/2022
Interim Report Submission (Year 3):	06/2023
Interim Report Submission (Year 4):	06/2024
Final Report Submission (Year 5):	06/2025

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
11/25/2019 10:26:50 AM

EXHIBIT 2

NDA 213137

ACCELERATED APPROVAL

Global Blood Therapeutics, Inc.
Attention: Linda Yokoshima
Senior Director, Regulatory Affairs
171 Oyster Point Boulevard, Suite 300
South San Francisco, CA 94080

Dear Ms. Yokoshima:

Please refer to your new drug application (NDA) dated June 26, 2019, received June 26, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OXBRYTA™ (voxelotor) tablets.

This new drug application provides for the use of OXBRYTA (voxelotor) tablets for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and for the Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on October 25, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213137**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for OXBRYTA was not referred to an FDA advisory committee because evaluation of the data did not raise significant safety or efficacy issues that were unexpected in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 22, 2019. This requirement, along with required completion dates, is listed below.

3746-1 Complete Study GBT440-032: the ongoing Phase 3, randomized, double-blind, placebo-controlled trial in pediatric patients (age 2 years to < 15 years) with Sickle Cell Disease (HOPE Kids 2). Expected enrollment of approximately 224 patients (age 2 years to < 15 years) with at least 15 patients from age 2 years to < 4 years of age. Include patients with baseline hemoglobin of less than 6 g/dL. The primary endpoint is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by transcranial doppler (TCD). The secondary endpoint is change from baseline in TCD flow velocity at Week 48 and Week 96.

Interim Report Submission (based on primary analysis):	07/2025
Study/Trial Completion:	03/2026
Final Report Submission:	09/2026

3746-2 Complete follow-up of patients (on treatment) enrolled in Study GBT440-031: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease (HOPE Trial). Conduct an updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Trial Completion:	12/2019
Final Report Submission:	09/2020

Submit clinical protocols to your IND 121691 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3746-3 Complete at least 5 years of follow-up for all patients (on treatment) enrolled in Study GBT440-034: An Open-Label Extension Study of voxelotor Administered Orally to Patients with Sickle Cell Disease who have Participated in GBT440 Clinical trials. Include updated safety and efficacy analysis in yearly reports and submit datasets at the time of final clinical study report submission.

The timetable you submitted on November 22, 2019, states that you will conduct this study according to the following schedule:

Interim Report Submission (Year 1):	06/2021
Interim Report Submission (Year 2):	06/2022
Interim Report Submission (Year 3):	06/2023
Interim Report Submission (Year 4):	06/2024
Final Report Submission (Year 5):	06/2025

Submit clinical protocols to your IND 121691 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[4]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Charlene Wheeler, Acting Chief Project Management Staff, Division of Hematology Products at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Deputy Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC R THEORET
11/25/2019 02:49:21 PM

EXHIBIT 3

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXBRYTA safely and effectively. See full prescribing information for OXBRYTA.

OXBRYTA™ (voxelotor) tablets, for oral use
Initial U.S. Approval: 2019

---------- INDICATIONS AND USAGE----------

OXBRYTA is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.

This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) (1).

----------DOSAGE AND ADMINISTRATION ----------

- Recommended dosage: 1,500 mg orally once daily with or without food (2.1).
- Recommended dosage for severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C) (2.2).

---------- DOSAGE FORMS AND STRENGTHS----------

Tablets 500 mg (3).

---------- CONTRAINDICATIONS ----------

Prior drug hypersensitivity to voxelotor or excipients (4).

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity Reactions: Observe for signs and symptoms and manage promptly (5.1).
- Laboratory Test Interference: Perform quantification of hemoglobin species when patient is not receiving OXBRYTA (5.2).

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence >10%) are headache, diarrhea, abdominal pain, nausea, fatigue, rash, and pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Global Blood Therapeutics, Inc. *1-833-GBT-4YOU (1-833-428-4968)* or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Sensitive CYP3A4 Substrates: Avoid co-administration of sensitive CYP3A4 substrates with a narrow therapeutic index (7.2).
- Strong CYP3A4 Inhibitors or Fluconazole: Avoid co-administration with strong CYP3A4 inhibitors or fluconazole. If unavoidable, reduce the dose of OXBRYTA (2.3, 7.1).
- Strong or Moderate CYP3A4 Inducers: Avoid co-administration with strong or moderate CYP3A4 inducers. If unavoidable, increase the dose of OXBRYTA (2.3, 7.1).

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage for Sickle Cell Disease
2.2 Recommended Dosage for Hepatic Impairment
2.3 Recommended Dosage with Concomitant Moderate or Strong Inducers, Strong Inhibitors of CYP3A4, or Fluconazole
3 DOSAGE FORMS AND STRENGTHS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OXBRYTA is indicated for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 years of age and older.

This indication is approved under accelerated approval based on increase in hemoglobin (Hb) *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Sickle Cell Disease

The recommended dosage of OXBRYTA is 1,500 mg taken orally once daily with or without food. If a dose is missed, continue dosing on the day following the missed dose.

Patients should swallow OXBRYTA tablets whole. Do not cut, crush, or chew the tablets.

OXBRYTA may be given with or without hydroxyurea.

2.2 Recommended Dosage for Hepatic Impairment

The recommended dosage of OXBRYTA in patients with severe hepatic impairment (Child Pugh C) is 1,000 mg taken once daily with or without food. No dosage adjustment of OXBRYTA is required for patients with mild or moderate hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage of OXBRYTA When Used with Concomitant Moderate or Strong Inducers, Strong Inhibitors of CYP3A4, or Fluconazole

Avoid concomitant use of strong or moderate CYP3A4 inducers, strong CYP3A4 inhibitors, or fluconazole with OXBRYTA *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*. If concomitant use of strong or moderate CYP3A4 inducers, strong CYP3A4 inhibitors, or fluconazole is unavoidable, adjust the OXBRYTA dosage as recommended in Table 1.

Table 1: OXBRYTA Recommended Dosage for Concomitant Medications

Concomitant Medication	Recommended OXBRYTA Dosage
Strong CYP3A4 inhibitors or fluconazole	1,000 mg once daily
Strong or moderate CYP3A4 inducers	2,500 mg once daily

3 DOSAGE FORMS AND STRENGTHS

Tablets: 500 mg light yellow to yellow, oval shaped, biconvex, debossed with “GBT 500” on one side.

4 CONTRAINDICATIONS

OXBRYTA is contraindicated in patients with a history of serious drug hypersensitivity reaction to voxelotor or excipients. Clinical manifestations may include generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia *[see Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions after administration of OXBRYTA have occurred in <1% of patients treated. Clinical manifestations may include generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia *[see Adverse Reactions (6.1)]*.

If hypersensitivity reactions occur, discontinue OXBRYTA and administer appropriate medical therapy. Do not reinitiate OXBRYTA in patients who experience these symptoms with previous use.

5.2 Laboratory Test Interference

OXBRYTA administration may interfere with measurement of Hb subtypes (HbA, HbS, and HbF) by high-performance liquid chromatography (HPLC) *[see Drug Interactions (7.3)]*. If precise quantitation of Hb species is required, chromatography should be performed when the patient is not receiving OXBRYTA therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is discussed in other sections of the labeling: Hypersensitivity Reactions *[see Contraindications (4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXBRYTA was evaluated in the HOPE trial based upon 88 patients who received OXBRYTA 1,500 mg and 91 patients who received placebo orally once daily *[see Clinical Studies (14)]*. Seventy-four patients received OXBRYTA 1,500 mg once daily for ≥24 weeks and 65 patients for ≥48 weeks.

In patients who received OXBRYTA 1,500 mg once daily the median age was 24 years (range:12-59); 65% female; 66% Black or African American and 23% Arab/Middle Eastern; and 65% receiving hydroxyurea at baseline.

Serious adverse reactions occurred in 3% (3/88) of patients receiving OXBRYTA 1,500 mg, which included headache, drug hypersensitivity, and pulmonary embolism occurring in 1 patient each. Permanent discontinuation due to an adverse reaction (Grades 1-4) occurred in 5% (4/88) of patients who received OXBRYTA 1,500 mg.

Dosage modifications (dose reduction or dosing interruption) due to an adverse reaction occurred in 41% (36/88) of patients who received OXBRYTA. Most frequent adverse reactions requiring dosage interruption occurring in more than one patient who received OXBRYTA 1,500 mg included diarrhea, headache, rash, and vomiting.

The safety profile observed in pediatric patients 12 to <17 years of age treated with OXBRYTA was similar to that seen in adult patients.

The most common adverse reactions occurring in ≥10% of patients treated with OXBRYTA 1,500 mg with a difference of >3% compared to placebo are summarized in Table 2.

Table 2: Adverse Reactions (≥10%) in Patients Receiving OXBRYTA with a Difference Between Arms of >3% Compared to Placebo in HOPE

Adverse Reaction [a]	OXBRYTA 1,500 mg (N=88)	Placebo (N=91)
Headache	23 (26%)	20 (22%)
Diarrhea	18 (20%)	9 (10%)
Abdominal Pain [b]	17 (19%)	12 (13%)
Nausea	15 (17%)	9 (10%)
Fatigue	12 (14%)	9 (10%)
Rash [c]	12 (14%)	9 (10%)
Pyrexia	11 (12%)	6 (7%)

[a] Adverse reactions were Grades 1 or 2 except for Grade 3 diarrhea (1), nausea (1), rash (1), and rash generalized (3)
[b] Abdominal pain (grouped PTs) included the following PTs: abdominal pain and upper abdominal pain
[c] Rash (grouped PTs) includes the following PTs: rash, urticaria, generalized rash, maculo-papular rash, pruritic rash, papular rash, erythematous rash, and vesicular rash

Clinically relevant adverse reactions occurring in <10% of patients included:

- Drug hypersensitivity

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Voxelotor

Strong CYP3A4 Inhibitors or Fluconazole

Co-administration of strong CYP3A4 inhibitors or fluconazole may increase voxelotor plasma concentrations and may lead to increased toxicity.

Avoid co-administration of OXBRYTA with strong CYP3A4 inhibitors or fluconazole and replace these drugs with alternative drugs when possible *[see Clinical Pharmacology (12.3)]*. Decrease the OXBRYTA dosage when co-administration with a strong CYP3A4 inhibitor or fluconazole is unavoidable *[see Dosage and Administration (2.3)]*.

Strong or Moderate CYP3A4 Inducers

Co-administration of strong or moderate CYP3A4 inducers may decrease voxelotor plasma concentrations and may lead to reduced efficacy.

Avoid co-administration of OXBRYTA with strong or moderate CYP3A4 inducers. Increase the OXBRYTA dosage when co-administration with a strong or moderate CYP3A4 inducer is unavoidable *[see Dosage and Administration (2.3)]*.

7.2 Effect of Voxelotor on Other Drugs

Voxelotor increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate) *[see Clinical Pharmacology (12.3)]*. Avoid co-administration of OXBRYTA with sensitive CYP3A4 substrates with a narrow therapeutic index. If concomitant use is unavoidable, consider dose reduction of the sensitive CYP3A4 substrate(s).

7.3 Laboratory Test Interference

OXBRYTA administration may interfere with measurement of Hb subtypes (HbA, HbS, and HbF) by HPLC *[see Warnings and Precautions (5.2)]*. If precise quantitation of Hb species is required, chromatography should be performed when the patient is not receiving OXBRYTA therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on OXBRYTA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of voxelotor to pregnant rats and rabbits during organogenesis at exposures up to 2.8-times (rats) and 0.3-times (rabbits) the exposure at the maximum recommended human dose resulted in no adverse developmental effects *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is approximately 14% and up to 43%, respectively. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

There are adverse effects on maternal and fetal outcomes associated with sickle cell disease in pregnancy *(see Clinical Considerations).* OXBRYTA should only be used during pregnancy if the benefit of the drug outweighs the potential risk.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women with sickle cell disease have an increased risk of adverse pregnancy outcomes for the mother and the fetus. Pregnant women are at greater risk for vasoocclusive crises, pre-eclampsia, eclampsia, and maternal mortality. For the fetus, there is an increased risk for intrauterine growth restriction, preterm delivery, low birth weight, and perinatal mortality.

Data

Animal Data

In embryo-fetal development studies, voxelotor was administered orally to pregnant rats at 15, 50, and 250 mg/kg/day (gestation days 7 through 17) and rabbits at 25, 75, and 150 mg/kg/day (gestation days 7 through 19) through organogenesis. Maternal toxicity was observed at the highest dose levels in these studies equivalent to 2.8-times (rats) and 0.3-times (rabbits) the exposures in patients receiving OXBRYTA at the recommended daily dose. There was no evidence of adverse developmental outcomes in rats or rabbits.

In a pre- and postnatal development study, voxelotor was administered orally to pregnant rats at 15, 50 and 250 mg/kg/day (gestation day 6 through lactation day 20). Maternal gestational body weights were decreased at 250 mg/kg/day, which continued to the end of lactation. The findings in offspring included reduced survival and reduced body weights throughout lactation, weaning and maturation. The effects in offspring were observed at the maternal dose of 250 mg/kg/day with an exposure approximately 2.8-times the exposure in patients at the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of voxelotor in human milk, the effects on the breastfed child, or the effects on milk production. Voxelotor was detected in milk in lactating rats. Plasma concentrations of voxelotor in pregnant rats were higher than the concentration in milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.
The concentration of voxelotor in animal milk does not necessarily predict the concentration of drug in human milk. Because of the potential for serious adverse reactions in the breastfed child, including changes in the hematopoietic system, advise patients that breastfeeding is not recommended during treatment with OXBRYTA, and for at least 2 weeks after the last dose.

8.4 Pediatric Use

The safety and effectiveness of OXBRYTA for sickle cell disease have been established in pediatric patients aged 12 years and older. Use of OXBRYTA for sickle cell disease is supported by evidence from an adequate and well-controlled study in adults and pediatric patients (HOPE trial). The HOPE trial enrolled a total of 26 pediatric patients aged 12 to <17 years, in

which 12 pediatric patients received OXBRYTA 1,500 mg once daily and 14 pediatric patients received OXBRYTA 900 mg once daily *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. The safety and efficacy of OXBRYTA in pediatric patients below the age of 12 years have not been established.

Pharmacokinetics, safety and efficacy in pediatric patients 12 years to <17 years were similar to that observed in adults *[see Dosage and Administration (2), Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The adverse reactions observed in pediatric patients 12 to <17 years treated with OXBRYTA were similar in type and frequency to those observed in adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Clinical studies of OXBRYTA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

Severe hepatic impairment increases voxelotor exposures *[see Clinical Pharmacology (12.3)]*. Reduce OXBRYTA dose *[see Dosage and Administration (2.2)]*.

11 DESCRIPTION

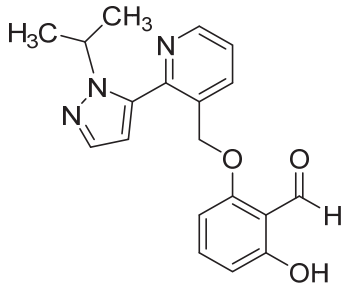
Voxelotor is a hemoglobin S polymerization inhibitor.

The chemical name of voxelotor is:

2-hydroxy-6-((2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde.

Voxelotor has a molecular formula of $C_{19}H_{19}N_3O_3$ and a molecular weight of 337.4.

The chemical structure of voxelotor is:



Voxelotor, the active drug substance, is a white-to-yellow-to-beige compound in crystalline Form II of its free base. It is non-hygroscopic. It is highly soluble in common organic solvents such as acetone and toluene and insoluble in water (approximately 0.03 mg/mL).

Each OXBRYTA film-coated tablet for oral use contains 500 mg of voxelotor with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. In addition, the film coating contains: polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Voxelotor is a hemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Nonclinical studies suggest that voxelotor may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity.

12.2 Pharmacodynamics

The pharmacodynamic effect of voxelotor treatment demonstrated a dose-dependent increase in Hb oxygen affinity as determined by the change in p50 (partial pressure of oxygen at which Hb oxygen saturation of 50% is achieved) that was linearly correlated with voxelotor exposure.

The pharmacodynamic effect of voxelotor treatment also demonstrated a dose-dependent reduction in clinical measures of hemolysis (indirect bilirubin and % reticulocytes).

Cardiac Electrophysiology

At plasma concentrations approximately 2-fold above therapeutic concentrations, voxelotor does not prolong QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Voxelotor is absorbed into plasma and is then distributed predominantly into RBCs due to its preferential binding to Hb. The major route of elimination of voxelotor is by metabolism with subsequent excretion of metabolites into urine and feces. The PK are linear and voxelotor exposures increased proportionally with either single or multiple doses (Table 3) in whole blood, plasma, and RBCs. Steady-state after repeated administration is reached within 8 days and exposures of voxelotor are consistent with accumulation predicted based on single dose data in patients with SCD.

Table 3: Pharmacokinetics Parameters of Voxelotor in Plasma and Whole Blood

PK Parameter	Voxelotor 1,500 mg Geometric Mean (%CV)
Plasma PK	
$AUC_{0\text{-}24h}$ (µg·hr/mL)	246 (27.7)
C_{max} (µg/mL)	12.6 (24.8)
Half-life (hours)	35.5 (25)
Whole Blood PK	
$AUC_{0\text{-}24h}$ (µg·hr/mL)	3820 (35)
C_{max} (µg/mL)	179 (33.1)

Absorption

The median plasma and whole blood T_{max} of voxelotor after oral administration is 2 hours. The mean peak concentrations in whole blood and RBCs are observed between 6 and 18 hours after oral administration.

Effect of Food

A high-fat, high-calorie meal increased voxelotor AUC by 42% and C_{max} by 45% in whole blood relative to AUC and C_{max} in the fasted state. Similarly, AUC increased by 42% and C_{max} increased by 95% in plasma.

Distribution

Voxelotor apparent volume of distribution of the central compartment and peripheral compartment are 338 L and 72.2 L in plasma, respectively. Protein binding is 99.8% in vitro. The blood-to-plasma ratio is approximately 15:1 in patients with SCD.

Elimination

The geometric mean (%CV) terminal elimination half-life of voxelotor in patients with SCD is 35.5 hours (25%) with concentrations in plasma, whole blood, and RBCs declining in parallel. The apparent oral clearance of voxelotor was estimated as 6.7 L/h in plasma in patients with SCD.

Metabolism

In vitro and in vivo studies indicate that voxelotor is extensively metabolized through Phase I (oxidation and reduction), Phase II (glucuronidation) and combinations of Phase I and II metabolism. Oxidation of voxelotor is mediated primarily by CYP3A4, with minor contribution from CYP2C19, CYP2B6, and CYP2C9.

Excretion

Following the administration of radiolabeled voxelotor, approximately 62.6% of the dose and its metabolites are excreted into feces (33.3% unchanged) and 35.5% in urine (0.08% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of voxelotor were observed based on age (12 to 59 years), sex, body weight (28 to 135 kg), or mild to severe renal impairment (creatinine clearance [CLcr] 15-89 mL/min).

Pediatric Patients

The pharmacokinetic parameters of voxelotor were similar in pediatric patients 12 to <17 years and adults.

Patients with Renal Impairment

There was no clinically significant effect of renal function on the excretion of voxelotor. Following a single 900 mg dose of voxelotor, whole blood exposures in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) were 25% lower compared to healthy controls.

The unbound plasma concentrations were comparable. OXBRYTA has not been evaluated in patients with end stage renal disease requiring dialysis.

Patients with Hepatic Impairment

The voxelotor AUC in whole blood were 14% and 15% higher in subjects with mild and moderate hepatic impairment (Child Pugh A and B) and 90% higher in subjects with severe hepatic impairment (Child Pugh C) compared to subjects with normal hepatic function.

Patients with HbSC Genotype

Voxelotor steady state whole blood AUC and C_{max} were 50% and 45% higher in HbSC genotype patients (n=11) compared to HbSS genotype (n=220) patients and voxelotor steady state plasma AUC and C_{max} were 23% and 15% higher in HbSC genotype patients compared to HbSS genotype patients.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Strong CYP3A4 Inhibitors on Voxelotor: concomitant use of OXBRYTA with ketoconazole is predicted to increase voxelotor AUC in patients by 42% to 83%.

Effect of Strong or Moderate CYP3A4 Inducers on Voxelotor: concomitant use of OXBRYTA with rifampin (a strong CYP3A4 inducer) is predicted to decrease voxelotor AUC in patients by up to 77%, and efavirenz (a moderate CYP3A4 inducer) is predicted to decrease voxelotor AUC in patients by up to 60%.

Effect of Fluconazole on Voxelotor: concomitant use of OXBRYTA with fluconazole, a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor, is predicted to increase voxelotor AUC in patients by 40% to 116%.

Effect of Acid Reducing Agents on Voxelotor: co-administration of omeprazole (proton pump inhibitor) with OXBRYTA did not alter voxelotor exposure.

Effect of Voxelotor on CYP450 Enzymes: in vivo voxelotor inhibits CYP3A4, but not CYP1A2, CYP2C9, CYP2C19, CYP2C8, or CYP2D6. The observed exposure increase of the CYP3A4 substrate midazolam in healthy subjects was 1.6-fold and the predicted increase in patients after multiple dosing is 2-fold.

Effect of Voxelotor on P-gp: concomitant use of OXBRYTA with digoxin (a P-gp substrate) did not alter digoxin to a clinically relevant extent.

In Vitro Studies

CYP Enzymes: voxelotor is a reversible and time-dependent inhibitor as well as an inducer of CYP2B6.

Transporter Systems: voxelotor is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K, or BSEP. Voxelotor is not a substrate of P-gp, BCRP, OATP1A2, OATP1B1, OATP1B3, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Voxelotor was not carcinogenic in a 26-week study in RasH2 transgenic mice at oral doses of 30, 150, or 500 mg/kg/day.

Voxelotor was not genotoxic in the reverse mutation bacterial (Ames) test, rat Comet assay, or rat micronucleus assay.

In a fertility and early embryonic development study, voxelotor was administered orally to rats at 15, 50, and 250 mg/kg/day. Males were dosed 28 days prior to mating through cohabitation and females were dosed 14 days prior to mating through gestation Day 7. Voxelotor had no effect on fertility or reproductive function. Sperm motility was decreased and changes in sperm morphology occurred at 250 mg/kg/day (approximately 5-times the human exposure at 1,500 mg/day).

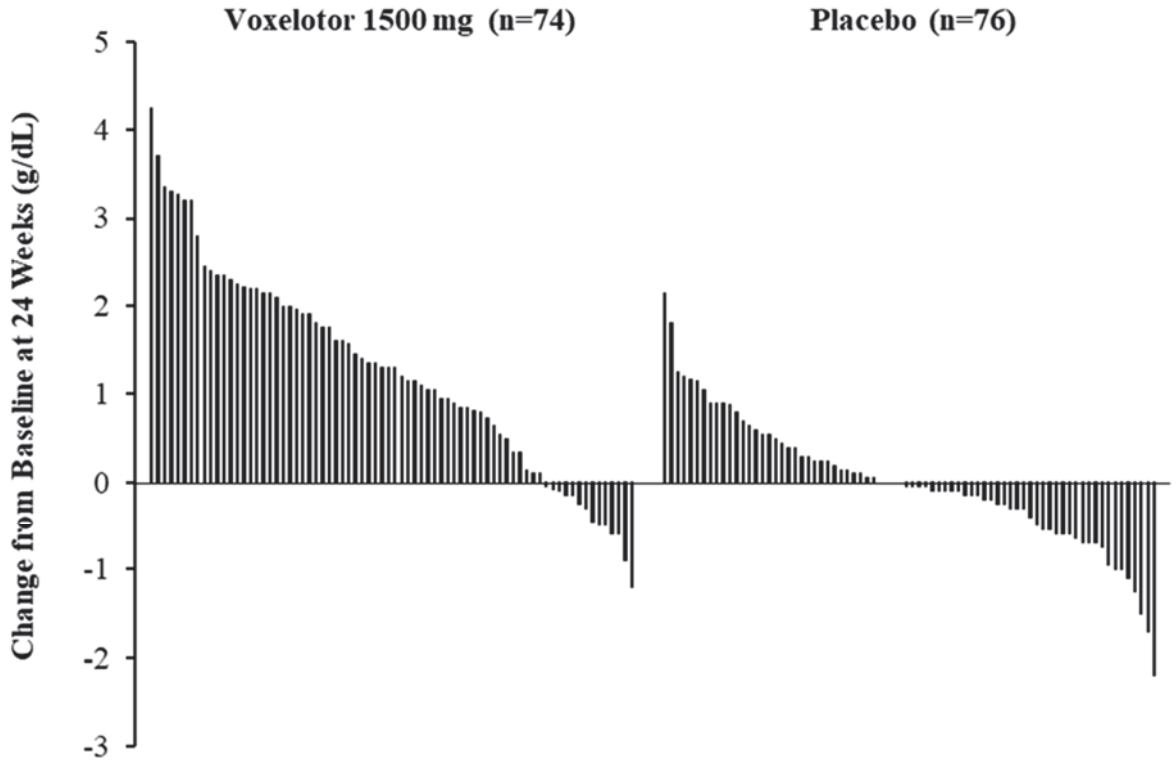
14 CLINICAL STUDIES

The efficacy and safety of OXBRYTA in sickle cell disease (SCD) was evaluated in HOPE, a randomized, double-blind, placebo-controlled, multicenter trial [NCT 03036813]. In this study, 274 patients were randomized to daily oral administration of OXBRYTA 1,500 mg (N=90), OXBRYTA 900 mg (N=92), or placebo (N=92). Patients were included if they had from 1 to 10 vasoocclusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. Randomization was stratified by patients already receiving hydroxyurea (yes, no), geographic region (North America, Europe, Other), and age (12 to <17 years, 18 to 65 years). The trial excluded patients who received red blood cell (RBC) transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating.

The majority of patients had HbSS or HbS/beta^0-thalassemia genotype (90%) and were receiving background hydroxyurea therapy (65%). The median age was 24 years (range: 12 to 64 years); 46 (17%) patients were 12 to <17 years of age. Median baseline Hb was 8.5 g/dL (5.9 to 10.8 g/dL). One hundred and fifteen (42%) had 1 VOC event and 159 (58%) had 2 to 10 events within 12 months prior to enrollment.

Efficacy was based on Hb response rate defined as a Hb increase of >1 g/dL from baseline to Week 24 in patients treated with OXBRYTA 1,500 mg versus placebo. The response rate for OXBRYTA 1,500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$). No outlier subgroups were observed. The distribution of Hb change from baseline for individual patients completing 24 weeks of treatment with OXBRYTA 1,500 mg or placebo is depicted in Figure 1.

Figure 1: Subject-level Change from Baseline in Hemoglobin at Week 24 in Patients Who Completed 24 Weeks of Treatment*



*Approximately 82% of all randomized patients completed 24 weeks of treatment.

Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to Week 24 (Table 4).

Table 4: Adjusted Mean (SE) Change from Baseline to Week 24 in Hemoglobin and Clinical Measures of Hemolysis

	OXBRYTA 1,500 mg QD (N=90)	Placebo (N=92)	P Value
Hemoglobin	1.14 g/dL (0.13)	-0.08 g/dL (0.13)	< 0.001
Indirect Bilirubin	-29.08 % (3.48)	-3.16 % (3.52)	< 0.001
Percent Reticulocyte Count	-19.93 % (4.60)	4.54 % (4.60)	< 0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

The 500 mg tablet is film-coated, light yellow to yellow, oval shaped, biconvex, debossed with "GBT 500" on one side, and available in:

- Bottles of 90 tablets with child-resistant closure: NDC 72786-101-01

The bottle also contains one desiccant canister and one polyester coil. Do not eat.

Store at or below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients that serious hypersensitivity reactions may occur, and to notify their healthcare providers if they develop generalized rash, urticaria, shortness of breath, facial swelling and eosinophilia *[see Warnings and Precautions (5.1)]*.

Advise women not to breastfeed while they are on OXBRYTA therapy *[see Use in Specific Populations (8.2)]*.

Dosage and Administration

Advise patients to:

- Continue taking OXBRYTA every day for as long as their physician tells them. This is a long-term treatment.
- Swallow OXBRYTA tablets whole. Do not cut, crush, or chew the tablets.
- Take with or without food.
- If a dose is missed, continue dosing on the day following the missed dose *[see Dosage and Administration (2.1)]*.

PATIENT INFORMATION
OXBRYTA™ (ox brye ta)
(voxelotor) tablets

What is OXBRYTA?

OXBRYTA is a prescription medicine used for the treatment of sickle cell disease in adults and children 12 years of age and older.
It is not known if OXBRYTA is safe and effective in children below 12 years of age.

Do not take OXBRYTA if you have had an allergic reaction to voxelotor or any of the ingredients in OXBRYTA.
See the end of this leaflet for a list of the ingredients in OXBRYTA.
If you are receiving exchange transfusions, talk to your healthcare provider about possible difficulties with the interpretation of certain blood tests when taking OXBRYTA**.**

Before taking OXBRYTA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- are pregnant or plan to become pregnant. It is not known if OXBRYTA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if OXBRYTA can pass into your breastmilk and if it can harm your baby. Do not breastfeed during treatment with OXBRYTA and for at least 2 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how OXBRYTA works. OXBRYTA may also affect how other medicines work.
Keep a list of all your medicines and show it to your healthcare provider.

How should I take OXBRYTA?

- Take OXBRYTA exactly as your healthcare provider tells you.
- Do not change your dose or stop taking OXBRYTA unless your healthcare provider tells you to.
- Take OXBRYTA 1 time each day. Swallow each OXBRYTA tablet whole. Do not cut, crush or chew the tablets.
  - Your healthcare provider may change your dose if needed.
- Your healthcare provider may also prescribe hydroxyurea during treatment with OXBRYTA.
- Take OXBRYTA with or without food.
- If you forget to take a dose of OXBRYTA, skip that dose and return to your normal dosing schedule the next day.

What are the possible side effects of OXBRYTA?

OXBRYTA can cause serious side effects, including:

- **Serious allergic reactions.** Tell your healthcare provider or get emergency medical help right away if you get:
  - rash
  - hives
  - shortness of breath
  - swelling of the face

The most common side effects of OXBRYTA include:

- headache
- diarrhea
- stomach (abdominal) pain
- nausea
- tiredness
- rash
- fever

These are not all the possible side effects of OXBRYTA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Global Blood Therapeutics, Inc. at 1-833-428-4968 (1-833-GBT-4YOU).

How should I store OXBRYTA?

- Store OXBRYTA at or below 86°F (30°C).
- OXBRYTA comes in a child-resistant package.
- The bottle contains a desiccant to help keep your medicine dry (protect it from moisture) and polyester coil. Do not eat.

Keep OXBRYTA and all medicines out of the reach of children.

General information about the safe and effective use of OXBRYTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OXBRYTA for a condition for which it was not prescribed. Do not give OXBRYTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about OXBRYTA that is written for health professionals.

What are the ingredients of OXBRYTA?

Active Ingredient: voxelotor
Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains: polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

Manufactured for: Global Blood Therapeutics, Inc. South San Francisco, CA 94080, USA.

OXBRYTA is a trademark of Global Blood Therapeutics, Inc.

 For more information, call 1-833-428-4968 (1-833-GBT-4YOU) or go to www.OXBRYTA.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 11/2019

EXHIBIT 4

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Labeling

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Labeling

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Contains Nonbinding Recommendations

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in developing the INDICATIONS AND USAGE section of labeling for human prescription drug and biological products that are approved under the accelerated approval regulatory pathway (hereafter accelerated approval) as defined in section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 314, subpart H, or 21 CFR part 601, subpart E. More specifically, this guidance focuses on indications for drugs[2] approved via accelerated approval on the basis of a surrogate endpoint or a clinical endpoint other than survival or irreversible morbidity.[3] This guidance also addresses labeling considerations for indications that were approved under accelerated approval and for which clinical benefit subsequently has been verified and the FDA terminates the conditions of accelerated approval under 21 CFR 314.560 or 21 CFR 601.46. In addition, this guidance addresses labeling considerations when the FDA withdraws approval of an indication that had been approved through the accelerated approval pathway while other indications for the drug remain approved.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] The term *drug* as used in this guidance refers to human drugs and biological products.

[3] This guidance focuses on indications that are granted accelerated approval status based on 21 CFR 314.510 and 21 CFR 601.41. This guidance does not address 21 CFR 314.520 and 21 CFR 601.42.

II. BACKGROUND

The accelerated approval process is one of several approaches used by the FDA to expedite the development of drugs for serious or life-threatening diseases and conditions. Section 506(c) of the FD&C Act provides that the FDA may grant accelerated approval to "a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." For purposes of this guidance, these categories of endpoints are referred to as surrogate endpoints and intermediate clinical endpoints.

This guidance focuses on how accelerated approval based on a surrogate endpoint, or on an intermediate clinical endpoint, is represented in the INDICATIONS AND USAGE section of labeling. In each case, the effect on the endpoint is established by the results of adequate and well-controlled clinical trials.[4] However, the accelerated approval is subject to the requirement that the applicant conduct additional postmarketing clinical trials to verify and describe the drug's clinical benefit,[5] where there is uncertainty as to the relationship of the surrogate endpoint to the clinical benefit, or of the intermediate clinical endpoint to ultimate outcome. Clinical benefit is verified when postmarketing clinical trials show that the drug provides a clinically meaningful positive therapeutic effect, usually an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.[6]

Labeling for human prescription drugs must contain "a summary of the essential scientific information needed for the safe and effective use of the drug."[7] Applications submitted for accelerated approval must include labeling that conforms to the content and format requirements for human prescription drug labeling delineated in 21 CFR 201.56(d) and 201.57. Labeling for drugs approved under the accelerated approval framework is in most ways the same as labeling for drugs with traditional approval.

However, if a drug is granted accelerated approval based on a surrogate endpoint, the INDICATIONS AND USAGE section of the labeling must also include a "succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical

[4] See 21 CFR 314.126.

[5] See section 506(c)(2)(A) of the FD&C Act; §§ 314.510 and 601.41.

[6] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/RegulatoryInformation/Guidances/default htm.

[7] See 21 CFR 201.56(a)(1).

benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence," as noted in § 201.57(c)(2)(i)(B).[8]

III. ACCELERATED APPROVAL LABELING CONSIDERATIONS

Certain special labeling considerations arise when the FDA approves a drug (or an indication) under the accelerated approval pathway, including the following: (1) information to be included in the INDICATIONS AND USAGE section of labeling; (2) revisions needed when postmarketing clinical trials have verified and adequately described the drug's clinical benefit for an indication granted under accelerated approval; and (3) revisions needed when the FDA withdraws approval of one or more indications granted under accelerated approval for a drug whose labeling includes other approved indications.

A. Indication Approved Under Accelerated Approval

Under FDA regulations, the information included in the INDICATIONS AND USAGE section of labeling for drugs approved under accelerated approval must include the indication (i.e., the disease or condition that the drug treats, prevents, mitigates, cures, or diagnoses),[9] as well as a "succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits. . . ."[10] The information in this section generally should also acknowledge that the drug was approved based upon accelerated approval and that continued approval for the drug (or indication) may be contingent upon verification and description of clinical benefit in a confirmatory trial or trials.

The following is an example of how these elements should be represented in the INDICATIONS AND USAGE section of the full prescribing information:

> DRUG X is indicated for {state indication}. This indication is approved under accelerated approval based on {state effect on surrogate endpoint or intermediate clinical endpoint that supported the accelerated approval} *[see Clinical Studies (14.X)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

A similar presentation should be used under the Indications and Usage heading in Highlights, except that the cross-reference to the CLINICAL STUDIES section is not necessary for Highlights.

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[8] The FDA interprets this provision as applying not only to drugs approved under accelerated approval on the basis of a surrogate endpoint, but also drugs approved under accelerated approval based on an effect on a clinical endpoint other than survival or irreversible morbidity. Under § 201.57(c)(2)(i)(B), the requirement to provide a succinct description of limitations of usefulness and any uncertainty about anticipated clinical benefits of a drug also applies to situations where "evidence is available to support the safety and effectiveness of a drug only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group). . . ."

[9] See § 201.57(c)(2).

[10] See § 201.57(c)(2)(i)(B).

A more detailed description of two elements of the INDICATIONS AND USAGE section is provided below with examples.

1. Limitations of Usefulness and Clinical Benefit Uncertainty

The INDICATIONS AND USAGE section for drugs (or indications) approved based on a surrogate or intermediate clinical endpoint should state the endpoint used in the clinical trials that provided substantial evidence to support accelerated approval, and the limitations of that endpoint. In addition, a cross-reference to the CLINICAL STUDIES section for a discussion of the available evidence should be included. The description of the basis for approval should immediately follow the indication rather than appear under a separate heading or paragraph.

The following is an example of a statement that states the endpoint used in the clinical trials to support the accelerated approval:

> This indication is approved under accelerated approval based on tumor response rate *[see Clinical Studies (14.1)]*.

Including the term *accelerated approval* is informative because it provides the framework and rationale for the other indication elements that are unique to drugs approved in this manner.

Simply reporting the endpoint used may convey sufficient information about uncertainty with regard to the limitations of usefulness of the drug and of uncertainty about anticipated clinical benefits (the benefit that is anticipated based upon the surrogate or intermediate clinical endpoint used to support accelerated approval). In other circumstances, additional context about the approval should be included in the indication by identifying the clinical outcome(s) that are expected (based on the effect demonstrated on the surrogate or intermediate clinical endpoint) but not yet established.

The following is an example of a statement that provides additional context about the approval by identifying the clinical outcome(s) that have not been established. Such information should be described immediately after the sentence that identifies the endpoint that supported accelerated approval.

> This indication is approved under accelerated approval based on a reduction in alkaline phosphatase *[see Clinical Studies (14.1)]*. An improvement in survival or disease-related symptoms have not been established.

2. Continued Approval

For indications approved under accelerated approval based on a surrogate or intermediate clinical endpoint, the applicant generally is required to conduct additional postmarketing clinical trials to verify and describe the drug's clinical benefit. Although regulatory postmarketing study requirements typically are not included in labeling, a brief summary of the confirmatory study requirements can further emphasize the limitations of the clinical study results supporting the

accelerated approval. Therefore, the INDICATIONS AND USAGE section should include a statement explaining that continued approval for the indication may be subject to the requirement that confirmatory trials verify the drug's clinical benefit. When summarizing the postmarketing study requirements, the statement should refer to *verification and description of clinical benefit* as described in the following example.

> Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

B. When Clinical Benefit Has Been Verified

Following successful verification and description of clinical benefit in the postmarketing studies, the information in the INDICATIONS AND USAGE section should be revised. The indication generally should reflect the population and condition for which there is substantial evidence of effectiveness, including any new or remaining limitations of use. The statements concerning limitations of usefulness and continued approval should be removed or revised, as appropriate. In addition, other sections of labeling (e.g., ADVERSE REACTIONS and CLINICAL STUDIES) should be revised, as appropriate, to reflect the new data (e.g., the CLINICAL STUDIES section generally should be revised to include a description of the clinical studies that verified clinical benefit).

C. Withdrawal of an Accelerated Approved Indication

Approval of a drug or indication approved under accelerated approval may be withdrawn either at the request of the applicant or by the FDA for the following reasons (among others):

- The applicant fails to conduct any required postmarketing study with due diligence
- A study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the drug fails to verify and describe such effect or benefit
- Other evidence demonstrates that the drug is not safe or effective under the conditions of use[11]

If the accelerated approval indication is withdrawn, but the drug remains approved for other indications, the labeling must be revised.[12] For example, it may be necessary to remove information concerning the withdrawn indication from several sections (e.g., INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES) so that the labeling does not imply or suggest that the drug is approved for the withdrawn indication.[13] In

[11] See section 506(c)(3) of the FD&C Act (21 U.S.C. 356(c)(3)); 21 CFR 314.530 and 601.43.

[12] See § 201.56(a)(2).

[13] See § 201.57(c)(2)(iv) and (v).

addition to removing information, it may sometimes be appropriate to add to the labeling new information concerning the withdrawn indication, as noted below.

1. Lack of Evidence Concerning the Withdrawn Indication

Under § 201.57(c)(2)(ii), if there is a common belief that the drug may be effective for a certain use, or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the drug do not generally outweigh its risks, the FDA may require that the INDICATIONS AND USAGE section state that there is lack of evidence that the drug is effective or safe for that use. When accelerated approval of an indication is withdrawn, the FDA may require that the labeling be revised to include a limitation of use concerning the withdrawn indication.[14]

2. Safety Information Concerning the Withdrawn Indication

Under § 201.57(c)(6)(i), a specific warning relating to a use not provided for under the INDICATIONS AND USAGE section may be required by the FDA in the WARNINGS AND PRECAUTIONS section of labeling if a drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard. Because the drug was previously indicated for the now-withdrawn use and may continue to be considered for that use by some health care providers, clinically significant adverse reactions or risks associated with the withdrawn indication may be appropriate to include in the WARNINGS AND PRECAUTIONS and/or ADVERSE REACTIONS sections of the revised labeling. The description of the risk or hazard also should be accompanied by a statement that the drug is not approved for the withdrawn indication.

[14] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/RegulatoryInformation/Guidances/default htm.

EXHIBIT 5

NDA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number	NDA 213137
Priority or Standard	Priority
Submit Dates	March 29, 2019, and June 26, 2019
Received Dates	March 29, 2019, and June 26, 2019
PDUFA Goal Date	February 26, 2020
Division/Office	Division of Hematology Products and the Office of Oncologic Diseases
Review Completion Date	November 24, 2019
Established/Proper Name	Voxelotor
(Proposed) Trade Name	OXBRYTA™
Pharmacologic Class	Hemoglobin S polymerization inhibitor
Code name	GBT440
Applicant	Global Blood Therapeutics, Inc. (GBT)
Dosage form	500 mg Tablets
Applicant proposed Dosing Regimen	1,500 mg orally once daily with or without food Recommended dosage for severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C)
Applicant Proposed Indication(s)/Population(s)	The treatment of sickle cell disease (SCD) in adult (b) (4) patients.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	417357006 Sickling disorder due to hemoglobin S
Recommendation on Regulatory Action	Accelerated Approval Indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older. This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Recommended Indication(s)/Population(s) (if applicable)	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	417357006

Recommended Dosing Regimen	Recommended dosage: 1,500 mg orally once daily with or without food Recommended dosage for severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C)

DHP obtained a consult from FDA's Interdisciplinary Review Team for QT Studies. See consult report from Dr Girish Bende in Darrts dated 08/23/2019. In summary, no significant QTc prolongation effect of voxelotor 1500 mg once daily was detected in this QT assessment.

Immunogenicity

Not Applicable

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Effect of Voxelotor on Tissue Oxygen Availability

Voxelotor (formerly known as GBT440), is a small-molecule HbS polymerization inhibitor developed for the treatment of adults and adolescents with SCD. Voxelotor' s mechanism of action is expected to specifically target the underlying mechanism of sickle cell disease by increasing the affinity of Hb for oxygen and stabilizing Hb in the oxyhemoglobin state and thereby inhibiting polymerization of HbS in RBCs. The Applicant hypothesizes that, by maintaining approximately 30% of Hb in the nonpolymerizing state, Voxelotor may be an effective therapeutic approach for SCD. This is supported by clinical data from Study A2201 which suggests voxelotor increases hemoglobin levels and decreases hemolysis, consistent with an inhibition of polymerization.

There is however a risk that at a certain percentage of Hb occupancy, offloading of O2 from voxelotor-bound Hb in the tissues could be decreased leading to possibly end-organ tissue hypoxia. In a recent article (Hebbel and Hedlund 2018), Hebbel and Hedlund express concern about whether the 30% modification by GBT440 would be protective for HbS polymerization under in vivo conditions since the 70% of Hb tetramers left unmodified by GBT440 still have normal ability to form polymers and the presence of the GBT440-modified tetramers would still contribute to cytoplasmic macromolecular crowding that magnifies the polymer formation by deoxyHbS. Therefore, the GBT440 effect will result in a significantly increased proportionate oxy-to-deoxyHb conversion, and no overall improvement in deoxyHbS concentration. The authors express further concern that, while the rising hemoglobin does increase blood viscosity, the modest increase in hb attained by voxelotor is inadequate to make up for the loss of 30% of oxygen delivery capability caused by giving the drug and the functional hemoglobin drop would be abrupt if full drug dosing is started immediately. Particularly in hypoxemic patients, the express concern that the GBT-modified tetramers would falsely bolster measured oxygen saturation measures, but this would not translate to oxygen delivery benefit and would be dangerous. Also, in sickle cell patients with marginal cerebrovascular blood the effect of the reduced functional oxygen content caused by voxelotor could enhance the cerebrovascular risk.

A commentary (Estepp 2018) in response to the article by Hebbel and Hedlund noted that, in two of seven patients with severe SCD who received voxelotor for up to 17 months under

GBT4040's compassionate use program, oxygenation improved after 24 weeks of voxelotor treatment. In one of these patients, One individual 6-minute walk tests were conducted at baseline and then following 14 and 24 weeks of voxelotor. During this interval, the 6-minute walk tests improved with declining pulse rates and rising SpO2 on room air.
In Study GBT031, severely anemic patients (Hb < 5.5 g/dL), were excluded. The median Hb in patients with SCD treated with voxelotor 1500mg and 900mg was 8.7g/dl and 8.3g/dl (range 5.9, 10.8) respectively.

FDA exploratory safety analyses did not find a difference in the safety profile in subjects more anemic at baseline.

No confirmed case of cerebrovascular injury occurred in Study GBT031. In the 90-Day safety update, the Applicant reported a possible treatment emergent CVA event and death in a 39-year-old male with HbSS sickle cell disease who had a history of 6 vaso-occlusive crisis the 12 months prior to study enrollment. The diagnosis of CVA in this patient was however unconfirmed and his death was attributed to encephalopathy due to multifocal intracerebral abscesses by the investigator. Further studies on the effect of voxelotor on cerebrovascular blood flow and oxygen delivery to the brain are warranted and will be required forvoxeletor as a confirmatory study.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

In the phase 3 Study GBT440-031, the Sickle Cell Disease Severity Measure (SCDSM), a self-administered 9-item subject questionnaire of SCD core symptoms, including pain severity, frequency, and type, as well as fatigue and mental acuity, on a 4-point response scale was completed daily using a handheld electronic device. The SCDSM was developed by the sponsor. Daily intake of prescribed study drug , use of opioid drugs, including the frequency and amount; and the days of school or work that were missed were recorded by subjects in an eDiary. Subjects also completed the EuroQol health questionnaire (EQ-5D-5L), standardized instrument for use as a measure of health outcome, at the start of clinic visits every 4 weekly and the investigator provided an assessment of the subject's overall condition using the Clinical Global Impression of Change (CGIC) at specific time points.

Rate of opioid use, changes in the SCDSM, EQ-5D-5L, CGIC and School and/or work attendance as recorded in the eDiary were evalutated as exploratory endpoints in Study 031 but did not inform safety/tolerability.

There were no additional COA data related to safety included in the application.

UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

RICKEY JOLLY, *et al.*, individually and on behalf of others similarly situated,

Plaintiffs,

v.

GLOBAL BLOOD THERAPEUTICS, INC. and PFIZER INC.,

Defendants.

Case No. 3:24-cv-09345-TLT

[PROPOSED] ORDER GRANTING DEFENDANTS' MOTION TO DISMISS THE FIRST AMENDED COMPLAINT

Date: July 8, 2025
Time: 2:00 P.M.
Location: Courtroom 9 – 19th Floor
450 Golden Gate Avenue
San Francisco, CA 94102

[PROPOSED] ORDER

The Motion to Dismiss the First Amended Complaint filed by Defendants Global Blood Therapeutics, Inc. and Pfizer Inc. came on regularly for hearing on July 8, 2025 in Courtroom 9, 19th Floor of the above-entitled Court.

The Court, having considered Defendants' Motion to Dismiss the First Amended Complaint, the Memorandum of Points and Authorities in support thereof, the Request for Judicial Notice in Support of the Motion to Dismiss, the Declaration of Teresa M. Wogoman, all other papers submitted in opposition and reply, the pertinent pleadings, and the applicable law, hereby **GRANTS** Defendants' Motion to Dismiss, without leave to amend, pursuant to Federal Rules of Civil Procedure 12(b)(1), 12(b)(6), and 9(b). Accordingly, it is hereby **ORDERED** that Plaintiffs' First Amended Complaint is **DISMISSED WITH PREJUDICE.**

IT IS SO ORDERED.

Dated: _____

_____
Hon. Trina L. Thompson
United States District Judge