REIMBURSEMENT GUIDE

ROCTAVIAN™ (valoctocogene roxaparvovec-rvox)

Indication

ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) is indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

Select Important Safety Information

Contraindications: Administration of ROCTAVIAN is contraindicated in

- patients with active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B)
- patients with known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent), or cirrhosis
- patients with known hypersensitivity to mannitol

ROCTAVIAN™
(valoctocogene roxaparvovec-rvox)
Suspension for intravenous infusion

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

BIOMARIN®

Table of contents

Introduction and disclaimer

Introduction

BioMarin, the manufacturer of ROCTAVIAN™ (valoctocogene roxaparvovec-rvox), would like to support every individual who is eligible and medically appropriate for gene therapy to help them gain access to it. We can provide patients, caregivers, and healthcare providers assistance with managing the process of gaining authorization to ROCTAVIAN treatment through our patient support program, **BioMarin RareConnections™**. We also work directly with patients and providers to help educate them before and after treatment day regarding the use of ROCTAVIAN.

Every patient's insurance plan and individual/family health benefits are different, so it is important to contact each patient's plan for assistance when interpreting drug policies, billing and coding, and payment. These items can vary greatly and are subject to change with or without notice (varies by plan) because of frequently changing guidelines, laws, rules, and regulations.

Additionally, some patients may change insurance plans during the year because of new life events and/or job changes, so verify current insurance information at each patient visit. If your patient encounters coverage issues or receives a denial for treatment, consult the insurance plan to help interpret the coverage policy and/or denial language, and provide the necessary information and documentation requested by the plan in a timely manner.

Disclaimer

While we have included some best practices for working with BioMarin RareConnections, insurance companies, and specialty pharmacies in this guide, BioMarin makes no guarantee that the use of this information will prevent denials, delays, or differences of opinion with insurance plans as to the correct information to submit for ROCTAVIAN authorization, or forms of billing that will expedite payment to providers of service. BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice.

Coding determinations are at the discretion of the provider and should be made in accordance with applicable regulations and payer guidance. Coverage and reimbursement may vary significantly by payer, plan, patient, and setting of care. It is the sole responsibility of the healthcare provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient. Providers should contact third-party payers for specific information on their coding, coverage, and payment policies. Information provided should in no way be considered a guarantee of coverage or reimbursement for any product or service.

This guide provides assistance for FDA-approved indications that are documented in the enclosed ROCTAVIAN Prescribing Information. Where reimbursement is sought for prescribed use and/or administration of this product that may be inconsistent with, or not expressly specified in, the FDA-cleared or FDA-approved labeling outlined in the ROCTAVIAN Prescribing Information, consult with your billing advisers or the patient's insurance plan on handling such issues.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

BioMarin RareConnections™

ROCTAVIAN™ Patient Support Program

BioMarin would like to guide you, your patient, and the HTC or infusion site through each step of the ROCTAVIAN treatment journey.

We offer product access support to patients, and education to caregivers, healthcare providers, and HTCs or infusion sites through BioMarin RareConnections.™
BioMarin RareConnections is a personalized product support program for patients with hemophilia A that helps them navigate access throughout their ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) treatment journey.

Our dedicated and experienced BioMarin RareConnections Case Managers (CMs) and Therapy Access Managers (TAMs) provide education to help gain access to ROCTAVIAN.

BioMarin RareConnections services include:

- Personalized patient support and education about ROCTAVIAN including what patients can expect pre- and post-infusion
- Education about eligibility and follow up testing for ROCTAVIAN including co-pay* programs for eligible commercially insured patients
  See pages 12 and 13 of this guide for important gene therapy eligibility/diagnostic testing information.
- Education about potential financial assistance options, including co-pay* assistance for gene therapy treatment and laboratory services

	CM	TAM
Patient enrollment	Program enrollment	N/A
	Testing information	
Education around securing coverage	Benefits investigation (BI)	Access
		Prior Authorization (PA)
	Prior Authorization (PA)	Appeals
Exploring financial assistance options†	Discuss options	Co-pay assistance
Product & pre-infusion coordination	Product coordination	Pre-infusion education
		Patient education
		Infusion site education
Post-infusion follow-up education	N/A	Follow-up reminders

*Valid only for those patients with commercial prescription insurance coverage for products who meet eligibility criteria. Offer not valid for prescriptions, administration, or related labs reimbursed, in whole or in part, by any federal, state, or government-funded insurance programs (for example, Medicare, Medicare Advantage, Medigap, Medicaid, VA, DoD, or TRICARE), for cash-paying patients, where product, administration, or related lab, are not covered by patient's commercial insurance, where patient's commercial insurance plan reimburses them for the entire cost of their prescription drug, administration, and/or related labs, or where prohibited by law or by the patient's health insurance provider. Patients who are residents of certain states (MA or RI) are not eligible for drug administration co-pay support. Patients who are residents of certain states (MI, MN, or RI) are not eligible for laboratory services co-pay support. If at any time a patient begins receiving prescription drug, administration, or related lab coverage under any such federal, state, or government-funded healthcare program, patient will no longer be able to use the BioMarin Co-Pay Assistance Program and patient must notify BioMarin RareConnections™ at 1-833-ROCTAVIAN (1-833-762-8284) to stop participation. Patients may not seek reimbursement for the value of the out-of-pocket expense amount covered by the Program from any third-party payer, whether public or private. The Program is valid ONLY for qualifying patients residing in the 50 U.S. states or in Puerto Rico with commercial insurance who have a valid prescription for an FDA-approved indication for the qualifying BioMarin therapy. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the Program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the Program without notice. Patient/caregiver certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. The Program is subject to termination or modification at any time. Some restrictions apply.

†As needed for eligible patients.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

BioMarin RareConnections™ (cont.)

Initiating support through BioMarin RareConnections

- **Enrolling your patients in BioMarin RareConnections early allows our team to provide support from the start, which could help expedite access to ROCTAVIAN™ (valoctocogene roxaparvovec-rvox). Visit BioMarin-RareConnections.com.**
- To explore financial options for eligible, commercially insured patients*, including lab testing support for patients, submit the Financial Support Program Form (FSF) along with front and back images of the patient's insurance card(s) and have your patient submit the Patient Consent Form (PCF). Patients can also submit the PCF at **ROCTAVIAN-PCF.com**.

  If you are ready to prescribe, and would like information about payer coverage and product coordination for the patient, submit the Patient Enrollment Form (PEF).

After submitting the PCF and the PEF and/or FSF, a BioMarin RareConnections CM will be assigned to you and your patient. The CM is the central point of contact for the access information. You will also have access to a TAM to assist you with any access and reimbursement education and will be the primary point of contact for the patient.

Case Manager (CM)

A BioMarin CM will be assigned to you and your patient. The CM is the central point of contact for the healthcare provider.

Name: _____

Phone: _____

Email: _____

Treatment Access Manager (TAM)

A TAM has a background in healthcare and is an expert in access and reimbursement. They can assist you with access and reimbursement education and will be the primary point of contact for the patient.

Name: _____

Phone: _____

Email: _____

BioMarin RareConnections Contact Information:

Phone: **1-833-ROCTAVIAN (1-833-762-8284)**

Hours: **Mon-Fri 8AM-8PM ET**

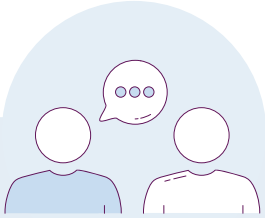
Fax: **1-833-979-2207**

BioMarin-RareConnections.com

*Valid only for those patients with commercial prescription insurance coverage for products who meet eligibility criteria. Offer not valid for prescriptions, administration, or related labs reimbursed, in whole or in part, by any federal, state, or government-funded insurance programs (for example, Medicare, Medicare Advantage, Medigap, Medicaid, VA, DoD, or TRICARE), for cash-paying patients, where product, administration, or related lab, are not covered by patient's commercial insurance, where patient's commercial insurance plan reimburses them for the entire cost of their prescription drug, administration, and/or related labs, or where prohibited by law or by the patient's health insurance provider. Patients who are residents of certain states (MA or RI) are not eligible for drug administration co-pay support. Patients who are residents of certain states (MI, MN, or RI) are not eligible for laboratory services co-pay support. If at any time a patient begins receiving prescription drug, administration, or related lab coverage under any such federal, state, or government-funded healthcare program, patient will no longer be able to use the BioMarin Co-Pay Assistance Program and patient must notify BioMarin RareConnections™ at 1-833-ROCTAVIAN (1-833-762-8284) to stop participation. Patients may not seek reimbursement for the value of the out-of-pocket expense amount covered by the Program from any third-party payer, whether public or private. The Program is valid ONLY for qualifying patients residing in the 50 U.S. states or in Puerto Rico with commercial insurance who have a valid prescription for an FDA-approved indication for the qualifying BioMarin therapy. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the Program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the Program without notice. Patient/caregiver certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. The Program is subject to termination or modification at any time. Some restrictions apply.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

BioMarin RareConnections™ (cont.)



Navigating the treatment journey

The **TAM** will reach out to your office to work directly with you and the HTC or infusion site to provide education around navigating the ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) gene therapy treatment journey. The TAM will also provide an in-depth review of this ROCTAVIAN Reimbursement Guide with you.

Support with the Benefits Investigation (BI), Prior Authorization (PA), and Appeals

The **CM** will send you notification of receipt of the FSF and PEF forms and request any missing or incomplete items. The CM will conduct and send the BI results, share PA forms and results, as well as discuss the distribution pathway options (SD and/or SP). The information will be sent to you in a document called the "BI/PA Summary Report."

The **TAM** will contact your patient to provide an in-depth overview of BioMarin RareConnections services during a welcome call. The TAM will provide the benefits investigation results to the patient after the provider has been notified by the CM. They will also discuss cost-sharing obligations related to ROCTAVIAN treatment, and discuss financial options, if needed.

If your patient is denied ROCTAVIAN treatment, the **TAM** will assist with providing education about appeal options. It's possible that your patient's insurance may exclude coverage for ROCTAVIAN, meaning they do not provide coverage at all for the treatment. BioMarin RareConnections will provide healthcare providers education on the appeals process, including appeals requirements based on your patient's plan.

Prior to providers submitting authorization paperwork to ensure a patient's eligibility for ROCTAVIAN, **the Hemophilia Treatment Center (HTC) or infusion site may need assistance with:**

- ordering
- coordinating shipping logistics for treatment day
- understanding coverage and reimbursement

You will also need to arrange for patient follow-up monitoring.

ROCTAVIAN™ treatment authorization

Requesting ROCTAVIAN™ treatment authorization from the patient's health insurance plan

Insurance Verification

When your patient arrives for their first visit to discuss ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) gene therapy, be sure to gather the following information, especially if they are a new patient or were referred to your office:

- Ask the patient/caregiver(s) for both primary and secondary insurance information
- Request complete contact information for patient and family/caregiver(s), including home, work, or cell phone numbers, and email addresses
- Copy/scan the front and back of the patient's medical and pharmacy insurance benefit cards

Prior Authorization (PA) and medical documentation

Every insurance plan is unique, and some plans may require additional verification steps to confirm that your patient is a candidate for ROCTAVIAN gene therapy. Some insurance plans may require the healthcare provider to confirm medical and treatment history, and diagnostic and baseline tests to establish medical necessity for treatment. Refer to the following page for a list of potential PA requirements for treatment authorization.

Single case agreements

Consider whether contracting with payers may be required on a per-patient basis.

ROCTAVIAN™ treatment authorization (cont.)

List of potential PA requirements

	✓	
Medical history		ICD-10 diagnosis
		Age eligibility (18 years old and above)
		Hemophilia A severity stratification
		FVIII inhibitor status
		Negative status for HBV and HCV active infections
Treatment history		Include patient's prior treatment information
Baseline testing (See page 12 for Eligibility Screening)		Factor VIII inhibitor titer testing
		Liver function tests
		Liver fibrosis assessment
		AAV5 DetectCDx™ antibody status
ROCTAVIAN information		ROCTAVIAN prescribing information
		Copy of ROCTAVIAN FDA approval letter

Medical necessity for ROCTAVIAN coverage

Most insurance plans will require a written request for treatment, usually called a Letter of Medical Necessity. This letter is written by the treating physician, and depending on the insurance plan, submitted along with the completed PA document and supporting medical documentation.

The insurance plan will review the completed Letter of Medical Necessity and/or PA and supporting medical documentation, and then provide a determination (an approval or denial) for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox).

An example Letter of Medical Necessity can be found on page 18.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

ROCTAVIAN™ treatment authorization (cont.)

Reviewing the insurance plan response for ROCTAVIAN™ treatment

When the insurance plan approves treatment, you'll work with BioMarin RareConnections™ to coordinate ordering of the product through either an Specialty Pharmacy (SP) or Specialty Distributor (SD). The TAM can work with the HTC regardless of the distribution pathway. If the insurance plan denies treatment, your TAM will reach out to discuss the denial, provide education around options for appealing the denial, if applicable, and provide continued education, if requested by the patient or healthcare provider.

Coverage determination

If the PA is approved, your CM and/or TAM will reach out to you to provide you with education around the patient's ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) treatment day. Payer follow-up stipulations will be uncovered in the PA process, including any required follow-up visits or assessments. They will also assist you if the PA is denied, and help you understand the treatment denial reason(s) and provide education around the options available to appeal the denial.

Monitor for any communication from the insurance plan and BioMarin RareConnections

There may be additional steps to determine whether a patient's insurance plan covers ROCTAVIAN.

Health insurance plans may request, as part of their authorization process, the following:

- companion diagnostic confirmation of a patient's antibody status
- baseline testing
- review of medical and treatment history
- confirmation of medical necessity
- authorization for treatment

See page 8 for a list of potential PA requirements.

Consider participating in payer gene therapy networks.

Payers may have particular requirements for gene therapy, **i.e.**, gene therapy networks, so consider reaching out to them to understand their requirements.

ROCTAVIAN™ treatment authorization (cont.)

Managing denials and appeals

Denials can occur when the:

- insurance plan does not provide coverage for a particular diagnosis
- insurance plan does not have enough information to confirm patient candidacy
- patient does not meet the clinical criteria for approval

Specialty drugs are commonly denied following an initial authorization request and will require submitting additional information, writing an appeal, or even conducting a discussion between the provider and the patient's insurance plan.

The insurance plan, by law, provides a written rationale for the denial to both prescriber and patient, usually by mail. Read these letters carefully, as they will provide the reasons for denial, methods for appealing the denial, and timeframe to request an appeal. If you do not understand the denial letter, contact the patient's insurance plan to request additional information.

TAMs can assist you with understanding the appeal options that may be available through the patient's insurance plan, if requested by the patient or healthcare provider.

Additional insurance plan requests

The denial letter may request additional information to ensure the patient qualifies for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox), including:

- Additional medical records
- Prior medication history
- Laboratory work
- Genetic testing records
- HCP's medical rationale for selecting ROCTAVIAN as medically necessary

If you receive a PA denial, BioMarin RareConnections will work with you to help understand why the PA request was denied

Evaluate the methods and timeframe for appealing (as stated in the denial letter) or contact the insurance plan directly to understand what additional information is being asked for and your appeal options. Written appeals are usually the first option provided, but if a peer-to-peer discussion is available, this can often be the preferred and most expeditious means of appealing a denial. The TAM is your resource to assist with education around appeals.

ROCTAVIAN™ treatment authorization (cont.)

Financial assistance

ROCTAVIAN Co-pay Assistance Program for eligible commercially insured patients

The ROCTAVIAN Co-Pay Assistance Program* is a BioMarin program that assists eligible, commercially insured patients with cost-sharing needs for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) treatment, including product, administration, and qualifying laboratory services for ROCTAVIAN pre-treatment eligibility testing and post-infusion monitoring. Once the FSF and PCF are submitted, the BioMarin RareConnections™ Case Manager can help educate the patient on their cost-sharing requirements and determine eligibility for the program. The program can cover up to 100% of co-pay/co-insurance and deductible costs depending on the patient's benefit design, up to the ROCTAVIAN Co-Pay Assistance Program's annual maximum benefit. The ROCTAVIAN Co-Pay Assistance Program is for commercially insured patients only, and certain terms and conditions may apply. HTCs, infusion sites, or providers that select to buy and bill will be able to submit patient-specific reimbursement requests to the program as well.

Independent foundation assistance

The **CM** can provide patients with a list of potential charitable organizations that may provide financial assistance to patients with hemophilia A. BioMarin does not influence or control the operations or eligibility criteria of any independent co-pay assistance foundation and cannot guarantee co-pay assistance after a referral to a charitable organization. This information is provided as a resource to patients. Please note that any list of charitable organizations is not indicative of BioMarin's endorsement or financial support of any disease area and/or foundation, nor is it exhaustive. There may be other foundations to support the patient's disease state.

Patients will need to contact these foundations directly for assistance. These foundations may have their own individual eligibility criteria, paperwork, and process, and will work with patients to determine if they qualify. For patients who qualify, they are approved for a specific time period, as determined by the foundation.

Ordering ROCTAVIAN

ROCTAVIAN is only available for order through an SP or SD and the **CM** assists with product coordination logistics through the SP or SD. The CM will confirm the location you selected for the patient's ROCTAVIAN treatment and ask you to choose an SP or SD to coordinate shipment, unless the patient's insurance plan design mandates a specific pharmacy. SP or SD selection may be dependent on the patient's insurance plan preference. The **TAM** helps with pre-infusion patient education and can also provide post-infusion follow-up reminders to patients for any follow-up labs that may be needed.

*Valid only for those patients with commercial prescription insurance coverage for products who meet eligibility criteria. Offer not valid for prescriptions, administration, or related labs reimbursed, in whole or in part, by any federal, state, or government-funded insurance programs (for example, Medicare, Medicare Advantage, Medigap, Medicaid, VA, DoD, or TRICARE), for cash-paying patients, where product, administration, or related lab, are not covered by patient's commercial insurance, where patient's commercial insurance plan reimburses them for the entire cost of their prescription drug, administration, and/or related labs, or where prohibited by law or by the patient's health insurance provider. Patients who are residents of certain states (MA or RI) are not eligible for drug administration co-pay support. Patients who are residents of certain states (MI, MN, or RI) are not eligible for laboratory services co-pay support. If at any time a patient begins receiving prescription drug, administration, or related lab coverage under any such federal, state, or government-funded healthcare program, patient will no longer be able to use the BioMarin Co-Pay Assistance Program and patient must notify BioMarin RareConnections™ at 1-833-ROCTAVIAN (1-833-762-8284) to stop participation. Patients may not seek reimbursement for the value of the out-of-pocket expense amount covered by the Program from any third-party payer, whether public or private. The Program is valid ONLY for qualifying patients residing in the 50 U.S. states or in Puerto Rico with commercial insurance who have a valid prescription for an FDA-approved indication for the qualifying BioMarin therapy. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the Program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the Program without notice. Patient/caregiver certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. The Program is subject to termination or modification at any time. Some restrictions apply.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Eligibility screening

Factor VIII inhibitor titer testing

These blood tests are used to detect factor VIII inhibitors. If these tests are positive, the patient will not be a candidate for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox).

Liver health

Baseline liver health assessments are required to confirm eligibility for ROCTAVIAN. These include:

- Liver function blood tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin and international normalized ration (INR)]
- Ultrasound and elastrography (e.g. FibroScan®) or laboratory assessments for liver fibrosis (e.g. FibroTest®, FibroSURE®), or similar.*

In case of radiological liver abnormalities and/or liver function test abnormalities (ALT, AST, GGT, ALP or total bilirubin > 1.25 X ULN or INR ≥ 1.4), consider a consultation with a hepatologist to assess eligibility for ROCTAVIAN.

AAV5 DetectCDx™

AAV5 DetectCDx* is a prescription-only companion diagnostic (CDx) test intended for detection of AAV5 antibodies in human plasma to aid in the selection of patients with hemophilia A for whom ROCTAVIAN treatment is being considered.

AAV5 DetectCDx is sponsored by BioMarin and offered at no cost to evaluate eligibility for an FDA-approved indication. While the assay is provided at no cost, shipping supplies and other expenses, charges, services, costs, materials, or lab work that are not provided by ARUP are not covered under this program.

No patient, private health plan, government health program, or any other individual or entity shall be billed for this serotype test, and no reimbursement will be sought for any tests or materials provided at no cost in connection with such test. Access to the test at no cost is not contingent upon the recommendation, ordering, prescription, or purchase of any other product or service.

Enrollment and eligibility requirements may apply, and BioMarin reserves the right to terminate or amend this program without notice at any time.

How to order the AAV5 DetectCDx test

If you are a hospital, health system, or reference laboratory that is partnered with ARUP, testing will be available through ARUP Connect™ or can be ordered with a manual client requisition. Test orders and results may also be built to electronically interface with your medical record and laboratory information systems.

Shipping

Ship the sealed kit via FedEx overnight or with an ARUP contracted courier.

Test requisition forms and collection kits can be obtained through **ARUP Client Services** (ARUP Supply Number 55016).

Call **1-800-522-2787** for more information or visit **www.aruplab.com/aav5**

*FibroTest® and FibroSURE® are registered trademarks of Laboratory Corporation of America® Holdings. FibroScan® is a registered trademark of Echosens North America Inc. AAV5 DetectCDx™ is a registered trademark of Associated Regional and University Pathologists, Inc.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Dosing guide: Calculating vials based on dose

ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) is administered as a one-time intravenous infusion of 6 × 10^{13} vector genomes per kilogram body weight.[1]

Example vial calculation[1]

Patient's weight in kg **x3=** **Patient's dose in mL** **÷8=** **Number of vials for exact dose** **Round up to the next whole number** **Total number of vials to order**

- The multiplication factor 3 represents the per-kilogram dose (6 x 10^{13} vg/kg) divided by the amount of vector genomes per mL of ROCTAVIAN suspension (2 x 10^{13} vg/mL)[1]
- The division factor 8 represents the minimum volume of ROCTAVIAN that is extractable from a vial (8 mL)[1]
- Be sure to round up the number of vials to order the correct amount of ROCTAVIAN for each patient[1]
- Dispose of unused product and disposable materials that may have come in contact with ROCTAVIAN in accordance with local guidance for pharmaceutical waste[1]
- Infusion-related reactions to ROCTAVIAN can have multiple manifestations (such as skin, mucosal, respiratory, gastrointestinal, cardiovascular manifestations, and pyrexia) and may require reduction in infusion rate, interruption of infusion, pharmacologic intervention, and prolonged observation[1]

1. ROCTAVIAN™ (valoctocogene roxaparvovec-rvox). Prescribing Information. BioMarin Pharmaceutical Inc.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Coding examples

The coding information provided is not comprehensive and is subject to change without notice. Providers are responsible for all coding determinations and submitting accurate claims for products and services rendered. Contact payers for specific information on their coding, coverage, and payment policies.

The following coding examples may not apply, are not inclusive of all potential codes that may be used, and are provided for consideration only.

Eligibility testing

ICD-10[1]	D66	Hereditary Factor VIII deficiency Classic hemophilia Deficiency Factor VIII (with functional defect) Hemophilia NOS Hemophilia A
CPT[2]	36415	Collection of venous blood by venipuncture
	76705	Ultrasound, abdominal, real time with image documentation; limited (e.g., single organ, quadrant, follow-up)
	80076	Hepatic function panel This panel must include the following: • Albumin (82040) • Bilirubin, total (82247) • Bilirubin, direct (82248) • Phosphatase, alkaline (84075) • Protein, total (84155) • Transferase, alanine amino (ALT) (SGPT) (84460) • Transferase, aspartate amino (AST) (SGOT) (84450)
	81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
	85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count
	85130	Chromogenic substrate assay
	85245	Clotting; factor VIII, VW factor, ristocetin cofactor
	85246	Clotting; factor VIII, VW factor antigen
	85247	Clotting; factor VIII, von Willebrand factor, and multimetric analysis
	85335	Factor inhibitor test
	86790	Antibody; virus, not elsewhere specified
	91200	Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report
Revenue Code[1]	0301	Laboratory: Chemistry
	0305	Laboratory: Hematology

1. CMS 2023

2. AMA CPT 2023. CPT codes, descriptions, and other data only are copyright 2023 American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association (AMA)

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Coding examples (cont.)

Infusion day

CPT[1]	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
	96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour
	99221	Initial hospital inpatient or observation care, per day, for the evaluation and management of a patient, which requires a medically appropriate history and/or examination and straightforward or low-level medical decision-making. When using total time on the date of the encounter for code selection, 40 minutes must be met or exceeded.
	99222	Initial hospital inpatient or observation care, per day, for the evaluation and management of a patient, which requires a medically appropriate history and/or examination and moderate level of medical decision-making. When using total time on the date of the encounter for code selection, 55 minutes must be met or exceeded.
	99223	Initial hospital inpatient or observation care, per day, for the evaluation and management of a patient, which requires a medically appropriate history and/or examination and high level of medical decision making. When using total time on the date of the encounter for code selection, 75 minutes must be met or exceeded.
	99234	Hospital inpatient or observation care, for the evaluation and management of a patient including admission and discharge on the same date, which requires a medically appropriate history and/or examination and straightforward or low level of medical decision-making. When using total time on the date of the encounter for code selection, 45 minutes must be met or exceeded.
Revenue Code[2]	0261	IV Therapy: Infusion Pump
	0290	Durable Medical Equipment (Other than Renal)
	0636	Pharmacy drugs requiring detailed coding
HCPCS[3]	C9399	Unclassified drug or biological
	E0780	Ambulatory infusion pump, mechanical, reusable, for infusion less than 8 hours
	J1412	Injection, valoctocogene roxaparvovec-rvox, per mL, containing nominal 2 × 10^13 vector genomes
	JW Modifier	Drug amount discarded/not administered to any patient
	When billing for ROCTAVIAN™ with a miscellaneous code, some insurance plans may require the following to be included in the free text areas of the billing form: **Name of drug:** ROCTAVIAN (valoctocogene roxaparvovec-rvox) **Amount of drug infused**: [xxx] mL infused Wastage: [xx] mL **Cost:** $	
NDC	68135-927-48	1 single-dose vial of ROCTAVIAN Note that the 10-digit NDC code for ROCTAVIAN is converted to an 11-digit billing format by inserting a zero in the second segment. The NDC code on the package is 68135-927-48; the 11-digit billing format is 68135-0927-48.

1. AMA CPT 2023. CPT codes, descriptions, and other data only are copyright 2023 American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association (AMA)
2. CMS 2023
3. CMS Level II HCPCS code file 2023

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Coding examples (cont.)

Post-infusion monitoring

CPT[1]	36415	Collection of venous blood by venipuncture
	80076	Hepatic function panel This panel must include the following: • Albumin (82040) • Bilirubin, total (82247) • Bilirubin, direct (82248) • Phosphatase, alkaline (84075) • Protein, total (84155) • Transferase, alanine amino (ALT) (SGPT) (84460) • Transferase, aspartate amino (AST) (SGOT) (84450)
	85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count
	85130	Chromogenic substrate assay
	85245	Clotting; factor VIII, VW factor, ristocetin cofactor
	85246	Clotting; factor VIII, VW factor antigen
	85247	Clotting; factor VIII, von Willebrand factor, and multimetric analysis
	85335	Factor inhibitor test
Revenue Code[2]	0305	Laboratory: Hematology

1. AMA CPT 2023. CPT codes, descriptions, and other data only are copyright 2023 American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association (AMA)

2. CMS 2023

The ROCTAVIAN™ Warranty

BioMarin is offering an innovative Warranty to all U.S. payers to remove barriers to access to ROCTAVIAN™ (valoctocogene roxaparvovec-rvox). This outcomes-based agreement between the participating payer and BioMarin is designed to address payer concerns about the initial response and durability of response for ROCTAVIAN.

Warranty criteria

The criteria of the Warranty are based on hemophilia-related metrics. These criteria include:

- Factor VIII levels – an objectively measurable biomarker
- Spontaneous bleeding events – a clinically relevant endpoint for hemophilia A
- Resumption of regular prophylaxis – a payer-focused utilization metric

The Warranty covers 4 years after administration of ROCTAVIAN.

The role of the site/Provider (HTC)

If a payer seeks payment from BioMarin under the terms of the Warranty, they may require certain information. You may be asked to provide specific information to a payer and/or BioMarin's third-party adjudicator in the event that a patient does not respond to ROCTAVIAN or loses response over time. Required documentation may include the prescriber information, patient information, Factor VIII levels, spontaneous bleeding events, an intent to resume continuous prophylaxis, and an attestation that the provider dosed, counseled, treated, and monitored the patient in a way that is consistent with ROCTAVIAN U.S. Prescribing Information.

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

Appendix

Possible enclosures:

- ROCTAVIAN FDA approval letter
- ROCTAVIAN Prescribing Information
- ROCTAVIAN published clinical studies
- Patient medical history, clinical notes, and labs confirming diagnosis
- Relevant labs, e.g., genetic tests, baseline testing

Sample letter of medical necessity for ROCTAVIAN™ gene therapy

Date:
Patient Name:
Patient Mailing Address:
Patient Contact Phone Number:
Insurance Plan Name:

Insurance Plan Mailing Address:
Insurance Subscriber Name:
Insurance Subscriber ID Number:
Effective Date of Coverage:

RE: Authorization of ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) Treatment

Dear Sir or Madam:

I am writing on behalf of my patient, **[insert patient name]**, to request approved authorization and coverage from **[insert insurance plan name]** for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) suspension for intravenous infusion. My patient has been diagnosed with severe hemophilia A and **[has been tested utilizing the AAV5 DetectCDx™ to show that s/he is negative for antibodies to adeno-associated virus serotype 5 (AAV5)]**. Based on my patient's treatment history and my professional medical opinion for the success of treatment, I believe that my patient is an excellent candidate for ROCTAVIAN gene therapy.

ROCTAVIAN is an AAV5 virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. Treatment with ROCTAVIAN consists of a single, intravenous infusion, which we plan to administer at **[insert Hemophilia Treatment Center or infusion site name]**. This letter provides information about my patient's medical and treatment history, diagnosis, and details regarding the medical necessity for treatment with ROCTAVIAN.

Patient medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that impact my treatment decision are:

- **[Insert brief description of patient: age, height, weight, hemophilia A severity status, FVIII inhibitor status, AAV5 antibody status, and prior treatment history]**
- **[Include essential labs and genetic history that verify severe hemophilia A diagnosis]**
- **[Include other factors that impact the treatment decision (e.g., comorbidities, work status, etc.)]**
- **[Include supporting medical documentation (e.g., patient medical record, clinical notes, medication records, relevant lab results (i.e., liver function tests (ALT, AST) and CPK)]**

Disease and Treatment Information

I have attached the prescribing information for ROCTAVIAN, which was approved by the U.S. Food and Drug Administration (FDA) on June 29, 2023.

ROCTAVIAN is dosed based on calculating the patient's body weight. The approved dose of ROCTAVIAN is 6×10^{13} vector genomes per kilogram (vg/kg) of body weight divided by the amount of vector genomes per mL of the ROCTAVIAN suspension (2×10^{13} vg/mL), and it is administered as a single intravenous infusion.

In conclusion, I am requesting that you approve treatment for my patient, **[insert patient name]**, with ROCTAVIAN. We are able to **[include details of proposed drug acquisition]**, and manage the administration and monitoring of ROCTAVIAN treatment at [insert name of Hemophilia Treatment Center or infusions site]. Please contact me with any additional questions or if you require additional information.

Sincerely,

[Insert prescriber name, credentials, contact information]

Appendix (cont.)

Possible enclosures:

- Copy of denial letter
- ROCTAVIAN Patient Enrollment or Patient Authorization form
- ROCTAVIAN Prescribing Information
- ROCTAVIAN published clinical studies
- Patient medical history, clinical notes, and lab results confirming diagnosis
- Relevant eligibility testing results

Sample appeal letter for ROCTAVIAN™ gene therapy

Date:
Patient Name:
Patient Mailing Address:

Patient Contact Phone Number:
Insurance Plan Name:
Insurance Plan Mailing Address:

Insurance Subscriber Name:
Insurance Subscriber ID Number:
Effective Date of Coverage:

RE: Appeal letter for denied authorization for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox)

Dear Sir or Madam:

I am writing on behalf of my patient, **[insert patient name]**, to appeal the **[insert date]** denial for coverage of ROCTAVIAN. My patient has severe hemophilia A. This letter provides the additional information requested by **[insert insurance plan name]** in the denial letter and is a formal request for appeal and expedited review of my request for ROCTAVIAN coverage for **[insert patient name]**.

Disease and treatment information

ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. This appeal letter provides additional information about my patient's medical and treatment history, diagnosis, and details regarding the medical necessity for treatment with ROCTAVIAN. ROCTAVIAN was approved by the U.S. Food and Drug Administration (FDA) on June 29, 2023.

Hemophilia A, also called Factor VIII deficiency or classic hemophilia, is an X-linked genetic disorder caused by missing or defective Factor VIII, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a new mutation that was not inherited. Approximately 1 in 10,000 people have hemophilia A.

I am requesting that you reassess the denial decision in light of the additional information I have provided and that you please approve my request for ROCTAVIAN treatment for **[insert patient name]**.

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that influence my treatment decision are:

- **[Insert brief description of patient: age, functional status, hemophilia history, and treatment history]**
- **[Include any additional lab results and genetic testing history that verify hemophilia diagnosis and demonstrate the patient's inability to produce protective Factor VIII levels that were not included with the original letter of medical necessity]**
- **[Include any additional supporting medical documentation (e.g., relevant excerpts from patient medical records, clinical notes, medication records, relevant lab results, etc.) that were not included with the original letter of medical necessity; include notes to support the patient's case]**
- **[Provide compelling medical rationale for selecting ROCTAVIAN as medically necessary treatment for your patient]**
- **[If patient has previously tried other therapies, it is helpful to include that information; indicate treatment failure or nonresponsiveness]**

In conclusion, I am asking **[insert insurance plan name]** to reconsider your decision to deny my patient access to ROCTAVIAN. I request that **[insert insurance plan name]** issue approval for the one-time gene therapy infusion.

Sincerely,

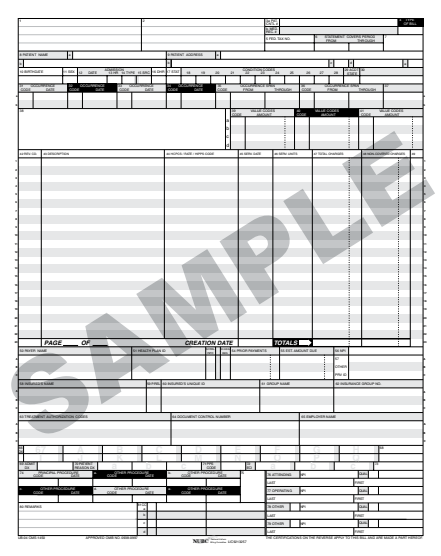
[Insert prescriber name, credentials, contact information]

Appendix (cont.)

Sample claim forms for ROCTAVIAN gene therapy

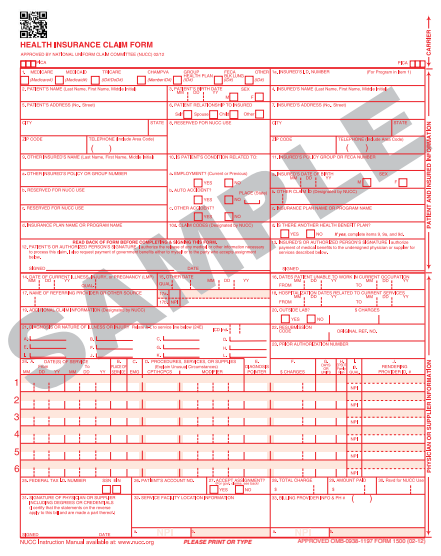
The coding and billing information provided is not comprehensive and is subject to change without notice. Providers are responsible for all coding determinations and submitting accurate claims for products and services rendered. Contact payers for specific information on their coding, coverage, and payment policies. The following coding and billing examples may not apply, are not inclusive of all potential codes that may be used, and are provided for consideration only.

Example for using the CMS 1450 (UB-04) claim form[1]



Field 38	Include HCPCS code and descriptor
Field 42	Include appropriate revenue code
Field 43	Include appropriate description of service
Field 44	Include appropriate HCPCS and CPT codes
Field 45	Include dates of service
Field 46	Include number of units of service
Field 63	Include prior authorization number
Field 66	Include the ICD-10 diagnosis code appropriate for the patient
Field 80	Include 11-digit NDC, unit of measure, and cost

Example for using the CMS 1500 claim form[1]



Field 19	Include HCPCS code, as well as 11-digit NDC, number of units administered, and route of administration
Field 21	Include the ICD-10 diagnosis code appropriate for the patient
Field 23	Include prior authorization number
Field 24A	Include dates of service
Field 24D	Include appropriate HCPCS and CPT codes
Field 24E	Include corresponding line item from Field 21 reflecting medical necessity
Field 24G	Include number of days or units of service

1. CMS 2023

Appendix (cont.)

Frequently used acronyms in the ROCTAVIAN™ Reimbursement Guide

AAV5	Adeno-associated virus serotype 5
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BI	Benefits investigation
CPK	Creatine phosphokinase
CM	Case Manager
FDA	United States Food and Drug Administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCP	Healthcare provider
HIV	Human immunodeficiency virus
HTC	Hemophilia Treatment Center
ICD-10	International Classification of Disease, Tenth Revision
PA	Prior Authorization
PAF	Patient Authorization Form
PEF	Patient Enrollment Form
SD	Specialty Distributor
SP	Specialty Pharmacy
TAM	Therapy Access Manager

Indication and Important Safety Information

ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) is indicated for the treatment of adults with severe hemophilia A (congenital Factor VIII deficiency with Factor VIII activity <1 IU/dL) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

Contraindications: Patients with active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B). Patients with known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent), or cirrhosis, and patients with known hypersensitivity to mannitol.

Infusion-related reactions including hypersensitivity reactions and anaphylaxis, have occurred. Monitor during and for at least 3 hours after ROCTAVIAN administration. Administer ROCTAVIAN in a setting where personnel and equipment are immediately available to treat infusion-related reactions. Discontinue infusion for anaphylaxis.

Hepatotoxicity: The safety and effectiveness of ROCTAVIAN in patients with hepatic impairment has not been established. Perform liver health assessments prior to administration. The majority of patients treated with ROCTAVIAN experienced ALT elevations and required corticosteroids for ALT elevation. Assess patient's ability to receive corticosteroids and/or other immunosuppressive therapy that may be required for an extended period. Live vaccines should not be administered to patients while on immunosuppressive therapy.

Monitor ALT weekly for at least 26 weeks and as clinically indicated, during corticosteroid therapy and institute corticosteroid treatment in response to ALT elevations as required. Continue to monitor ALT until it returns to baseline. Monitor Factor VIII activity levels since ALT elevation may be accompanied by a decrease in Factor VIII activity. One case of autoimmune hepatitis was reported during third year follow-up in a patient with history of hepatitis C and steatohepatitis.

It is recommended that patients abstain from consuming alcohol for at least 1 year after administration and thereafter limit alcohol use. Concomitant medications may cause hepatotoxicity, decrease Factor VIII activity, or change plasma corticosteroid levels which may impact liver enzyme elevation and/or Factor VIII activity or decrease the efficacy of the corticosteroid regimen or increase their side effects. Closely monitor concomitant medication use including herbal products and nutritional supplements and consider alternative medications in case of potential drug interactions.

Thromboembolic Events: Factor VIII activity above ULN has been reported following ROCTAVIAN infusion. Thromboembolic events may occur in the setting of elevated Factor VIII activity above ULN. Evaluate patients for risk of thrombosis including general cardiovascular risk factors before and after administration of ROCTAVIAN. Advise patients on their individual risk of thrombosis in relation to their Factor VIII activity levels above ULN and consider prophylactic anticoagulation. Advise patients to seek immediate medical attention for signs or symptoms indicative of a thrombotic event.

Factor VIII Inhibitors and Monitoring for Inhibitors. The safety and effectiveness of ROCTAVIAN in patients with prior or active Factor VIII inhibitors have not been established. Patients with active Factor VIII inhibitors should not take ROCTAVIAN. Following administration, monitor patients for Factor VIII inhibitors (neutralizing antibodies to Factor VIII). Test for Factor VIII inhibitors especially if bleeding is not controlled, or plasma Factor VIII activity levels decrease.

Please see additional safety information in the Prescribing Information.

Indication and Important Safety Information (cont.)

Monitor Factor VIII using the same schedule for ALT monitoring. It may take several weeks after ROCTAVIAN infusion before ROCTAVIAN-derived Factor VIII activity rises to a level sufficient for prevention of spontaneous bleeding episodes. Exogenous Factor VIII or other hemostatic products may also be required in case of surgery, invasive procedures, trauma, or bleeds. Consider more frequent monitoring in patients with Factor VIII activity levels ≤5 IU/dL and evidence of bleeding, taking into account the stability of Factor VIII levels since the previous measurement.

Factor VIII activity produced by ROCTAVIAN in human plasma is higher if measured with one-stage clotting assays compared to chromogenic substrate assays. When switching from hemostatic products prior to ROCTAVIAN treatment, physicians should refer to the relevant prescribing information to avoid the potential for Factor VIII activity assay interference during the transition period.

Malignancy: The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. ROCTAVIAN can also insert into the DNA of other human body cells. Monitor patients with risk factors for hepatocellular carcinoma (eg, hepatitis B or C, nonalcoholic fatty liver disease, chronic alcohol consumption, nonalcoholic steatohepatitis, advanced age) with regular liver ultrasound (eg, annually) and alpha-fetoprotein testing for 5 years following ROCTAVIAN administration. In the event that any malignancy occurs after treatment with ROCTAVIAN, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100.

Most Common Adverse Reactions: Most common adverse reactions (incidence ≥5%) were nausea, fatigue, headache, infusion-related reactions, vomiting, and abdominal pain. Most common laboratory abnormalities (incidence ≥10%) were ALT, AST, LDH, CPK, Factor VIII activity levels, GGT, and bilirubin >ULN. Patients also experienced adverse reactions from corticosteroid use.

Isotretinoin, Efavirenz, and HIV-Positive Patients. Isotretinoin is not recommended in patients who are benefiting from ROCTAVIAN. Efavirenz is not recommended in patients treated with ROCTAVIAN. Clinical studies of ROCTAVIAN did not include sufficient numbers of patients with HIV to determine whether the efficacy and safety differs compared to patients without HIV infection.

Females and Males of Reproductive Potential. ROCTAVIAN is not intended for administration in women. There are no data on the use of ROCTAVIAN in pregnant women or regarding lactation. For 6 months after administration of ROCTAVIAN, men of reproductive potential and their female partners must prevent or postpone pregnancy using an effective form of contraception, and men must not donate semen.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to BioMarin Pharmaceutical Inc. at 1-866-906-6100.

Please see additional safety information in the Prescribing Information.

ROCTAVIAN™

(valoctocogene roxaparvovec-rvox)

Suspension for intravenous infusion

Please visit ROCTAVIAN.com/hcp for more information

Please see Important Safety Information on page 22-23 and in the Prescribing Information.

BIOMARIN®