Drug Use Research & Management Program
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New Drug Evaluation: Valoctocogene suspension for intravenous infusion

Date of Review: October 2023
End Date of Literature Search: 07/14/2023
Generic Name: valoctocogene roxaparvovec-rvox
Brand Name (Manufacturer): Roctavian (Biomarin Pharmaceutical Inc.)

Dossier Received: yes

Plain Language Summary:

- Hemophilia A is an inherited disorder in which blood does not clot properly due to a lack of clotting factor VIII. This results in uncontrolled bleeding from cuts or injuries, unexplained nosebleeds, and many large bruises. Some patients bleed unexpectedly into joints without having an injury. This condition mostly affects males assigned at birth. Patients are usually given replacement clotting factor to prevent or treat bleeding.
- Valoctocogene roxaparvovec-rvox is a new gene therapy used to increase factor VIII (a part of the blood that helps a person stop bleeding) and to reduce bleeding in adults with severe hemophilia A. The new gene to make factor VIII must go through steps in the liver to work.
- One small study shows that valoctocogene roxaparvovec-rvox increases the factor VIII activity in many patients enough to reduce or eliminate need for replacement factor VIII products and reduce the number of bleeds that have to be treated with factor VIII products. This treatment remains effective for up to two years. We do not known how long this treatment remains effective beyond two years.
- Most patients had signs of liver damage after receiving this treatment. This may also put the patient at risk of having less benefit from the gene therapy effect of factor VIII. Patients who experienced this had to take corticosteroids for 2 months or longer until lab tests were back to normal and so that the treatment could continue to work.
- Gene therapies are a newer type of treatment. People who receive this therapy must be monitored for new cancers over time, especially liver cancer, because of possible risks.
- Some people with Hemophilia A have immune systems that have created certain types of inhibitors or antibodies, and they should not get this gene therapy because they will not receive benefit.
- Providers must explain to the Oregon Health Authority why someone needs valoctocogene roxaparvovec-rvox before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of valoctocogene roxaparvovec-rvox for hemophilia A?
2. What are the harms of valoctocogene roxaparvovec-rvox for hemophilia A?
3. Are there any important subgroups of patients where valoctocogene roxaparvovec-rvox has not been studied or may have different effects?

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Conclusions:

- There is low quality evidence based on one poor quality, open-label, single-arm, phase 3 trial with 2 year extension in patients with severe hemophilia A that valoctocogene roxaparvovec-rvox treatment increased factor VIII activity levels at week 49-52 after treatment compared to baseline levels (mean change: 41.9 IU/dL [95% confidence interval [CI] 34.1 to 49.7; P<0.001]). Annualized treated bleeding rates were also improved after 4 to 52 weeks (Change -4.1 bleeds/yr [95% CI, -5.3 to -2.8; P<0.001]) and 104 weeks post treatment (Change -4.1 bleeds/yr [95% CI, -5.3 to -2.98; P<0.001]) compared to baseline.[1,2] Evidence quality for outcome and trial were downgraded due to risk of bias.
- All patients enrolled in the trial experienced adverse reactions and 16.4% experienced serious adverse reactions. Alanine aminotransferase (ALT) increase was the most common adverse reaction and 79.1% of patients received glucocorticoids (median 230 days) in accordance with the study protocol. Therapeutic prednisone 60 mg daily, tapered over a minimum of 8 weeks, was used to protect gene transduced hepatocytes and maintain factor VIII expression.[2]
- Data are limited for use in people with risk factors for, or preexisting hepatic dysfunction.[2]

Recommendations:

- Implement prior authorization to ensure safe and appropriate use.
- Maintain valoctocogene roxaparvovec-rvox as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).

Background:

Hemophilia A is a recessive, bleeding disorder that is linked to the X chromosome and primarily affects males assigned at birth.[3] Hemophilia A represents a deficiency in clotting factor VIII and affects 1 in 5,000 live male births.[4] Females assigned at birth are more likely to experience mild or moderate hemophilia A.[3] Bleeding most often occurs in large joints, leading to hemophilic arthropathy, which results in significant pain and physical disability.[3,4] Physical activity can greatly increase the risk for weight-bearing joint bleeds, and as a result, many people with hemophilia avoid sports, exercise, and physical activities.[3] Risk of bleeding associated with physical activity and frequent infusions of on-demand and prophylactic clotting factor concentrates (CFCs) contribute to the reduced quality of life (QoL) in individuals with hemophilia A.[3] The severity of hemophilia A is defined by percent of normal clotting factor level. Factor VIII activity of less than 1% or less than 0.01 unit/mL is considered severe and places individuals at risk of spontaneous bleeding.[4] Factor VIII activity of 1-5% is moderate with occasional spontaneous bleeding and prolonged bleeding with surgery or minor trauma.[4] Those with mild hemophilia A have a factor VIII level of 5% to 40% and may experience severe bleeding after surgery or major trauma, but risk of spontaneous bleeding is low.[4]

The current standard of care for severe hemophilia A is regular administration of prophylactic CFCs or other hemostasis products to prevent bleeding.[3] This prophylaxis is recommended prior to the age of 3 years to prevent both acute bleeds and the long-term development of hemarthroses and joint disease.[3] Many CFCs have a short half-life, leading to breakthrough bleeding as factor levels fall close to baseline between intravenous administration of factor VIII.[3] Newer formulations of CFCs with an increased half-life and the use of monoclonal antibodies allow for extended intervals between administrations. Some patients develop inhibitors to factor VIII and require other therapy such as emicizumab.[4] Outcomes used when caring for patients and researching interventions for hemophilia A tend to include annualized bleeding rate (ABR), response to treatment (e.g., number of CFC infusions or dose required to resolve a bleed or time from last infusion to bleeding episode), need for other therapies, and quality of life.[3] There are no clear minimum clinically important differences (MCIDs) for these outcomes. The Haem-A-Qol is a common questionnaire used for assessment of health-related quality of life.[5] It has been validated in adult patients ≥ 17 years old with hemophilia.[5] Questions use a 5-point Likert-type frequency scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time).[5] Higher total scores indicate more impairment and the maximum score is 100.[5] There are 10 different domains (e.g., physical health, sports & leisure, work & school) with varying numbers of items in each domain.[5]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Valoctocogene roxaparvovec-rvox (ROCTAVIAN) is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with severe hemophilia A, with factor VIII activity < 1 IU/dL without pre-existing adeno-associated virus serotype 5 (AAV5) antibodies detected by a Food and Drug Administration (FDA)-approved test.[6] The functional copy of a transgene is transcribed in the liver hepatocytes with a liver-specific promoter to result in the expression of the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). The hFVIII-SQ is meant to replace the missing coagulation factor VIII in people with hemophilia A.[6]

Valoctocogene roxaparvovec-rvox approval was based on one trial (GENEr8-1) in adult men (n=134) with severe hemophilia A (factor VIII activity < 1 IU/dL).[2] Those with factor VIII inhibitors, AAV5 antibodies, and risk factors or active liver disease were excluded.[2] Patients with human immunodeficiency virus (HIV) were excluded by protocol amendment after hepatoxicity was seen in a patient on efavirenz in a different valoctocogene study (**Table 2)**.[2] This single-arm, open-label, multi-center phase 3 study assessed the effect of a single-infusion gene therapy treatment in improving factor VIII activity levels during weeks 49 to 52 post-infusion compared to a baseline period as the primary endpoint.[2] Additional endpoints included annualized factor VIII use and annualized treated bleeding rate. Baseline levels for these were determined using historical medical records or information gathered during the 270-902 study. After gene therapy treatment, the factor VIII use and the number of bleeding episodes requiring factor VIII treatment were patient reported at each visit as captured in patient diary. Baseline factor VIII use and bleeding episodes in a subset of the modified intent-to-treat population came from study records in patients who had rolled over from the non-interventional 270-902 study and had at least 6 months of data. [2] This non-interventional study prospectively recorded bleeding episodes, factor VIII infusion information, and patient reported outcomes in severe hemophilia A patients and had the same study sponsor as the GENEr8-1 trial. At baseline, most patients had zero (72.4%) or one (12.7%) problem joint. Enrolled patients had a median of 121.1 factor VIII infusions and 2.3 bleeds annualized each year. The annualized mean rate for factor infusion and bleeds were higher than the median (137.5 infusions/year and 5.4 bleeds/year) which may indicate a skewed population distribution or outliers with more frequent bleeding and infusions.[2] Two patients with HIV were enrolled prior to the protocol change, and 14.9% and 30.6% had a history of hepatitis B and C infections, respectively.[2] All participants were male sex and primarily White (71.6%).[2]

The modified intent-to-treat (mITT) population included all patients receiving valoctocogene roxaparvovec-rvox and without HIV. At week 49 to 52, the average factor VIII activity level was improved from less than 1 IU/dL at baseline to a mean of 42.9 IU/dL (standard deviation [SD] 45.5) and median of 23.9 IU/dL (interquartile range 11.9 to 62.3).[2] The secondary endpoints assessed in the rollover population found a 98.6% decrease (P<0.001) in mean annualized factor VIII concentrate use and mean change in bleeds of -4.1 annualized bleeds/yr (95% CI -5.3 to -2.8; P<0.001).[2]

An extension trial of the GENEr8-1 study reported outcomes out to week 104 where 132 of the original 134 participants remained in the study.[1] Based on feedback from the FDA, the primary endpoint of this 2-year extension analysis was amended to evaluate change in annualized treated bleeding events instead of factor VIII activity.[1] In people with data on factor utilization prior to treatment (n=112), the annualized bleeding rate compared to baseline was improved by an average of -4.1 bleeds/yr (95% CI -5.3 to -2.98, P<0.001) at 104 weeks.[1]

Studies are ongoing to evaluate continued durability of response over time and monitor for unknown side effects which could occur as gene therapy treatments are used more widely in clinical practice.[1] This trial was limited by the open-label, single arm design. Additionally, some outcomes such as factor VIII consumption from on demand use and treated bleeding events require a subjective assessment which increase risk of bias for this trial. The exclusion criteria around hepatotoxicity make safety and effectiveness uncertain in people with risk factors for liver injury. Those with increased alanine aminotransferase (ALT) who received glucocorticoids to protect against potential cytotoxicity did not seem to have reduced factor VIII activity compared to those who did not experience ALT increases. Valoctocogene roxaparvovec-rvox should not be used in those with pre-existing factor VIII inhibitors or AAV5 antibodies as therapy will not be effective for people with these characteristics.

Clinical Safety:

Valoctocogene roxaparvovec-rvox has contraindications for use with active infections (acute or chronic), known significant hepatic fibrosis or cirrhosis, or those with known hypersensitivity to mannitol.[6] Every participant experienced at least one adverse reaction; most were mild while 16.4% experienced serious adverse reactions.[2] Rise in ALT occurred in 85.8% of patients. There is concern that transduced hepatocytes may become targets for cellular cytotoxicity.[7] This appears to result in increased ALT and potential loss of transgene expression.[7] A glucocorticoid protocol, used to mitigate these concerns, was initiated in 79.1% of patients. In addition, 29.1% of patients received other immunosuppressants due to contraindications, side effects, or a poor/absent response from glucocorticoid treatment.[2] Eleven patients (8.2%) had a grade 3 ALT increase and 2 of these patients experienced serious elevations and required intravenous methylprednisolone.[2] The median corticosteroid treatment duration was 230 days, with 71.8% of patients receiving corticosteroids experiencing typical glucocorticoid side effects (e.g., Cushing's syndrome, acne, insomnia).[2] There were no deaths or withdrawals due to adverse events.[2] No patients reported thromboembolism although this is a hypothetical risk with increased factor levels and was included as a precaution in the product labeling.[6] Additional labeled warnings include theoretical risk of hepatocellular carcinoma and significant differences with measurements of factor VIII activity based on laboratory assay type and the reagents used. When transitioning from hemostatic agents, after receipt of valoctocogene roxaparvovec-rvox, patients should have factor VIII levels consistently measured with the same type of test and same reagents when possible.[2] More common adverse reactions include headache, nausea, vomiting, abdominal pain, and fatigue.[6] **Table 2** describes additional details of the phase 3 clinical trial including efficacy and safety data.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Clinically relevant bleeds
2) Quality of Life
3) Freedom from prophylactic factor therapy infusions
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in Factor VIII activity over 49 to 52 weeks

Table 1. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	• Adeno-associated virus serotype 5 (AAV5) based gene therapy vector. • Introduces a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). • Transcription of this transgene occurs within the liver resulting in the expression of hFVIII-SQ, which replaces the missing coagulation factor VIII.
Biodistribution	• Peak vector deoxyribonucleic acid (DNA) and shedding between days 1 to 9 post-dose and detectable in plasma up to 10 weeks.
Distribution and Protein Binding	• Highest vector DNA concentration in blood, followed by saliva, semen, stool, and urine.

Elimination	• For encapsidated (potentially transmissible) vector DNA, maximum time to first of 3 consecutive measurements below limit of detection or negative by the time of data cut was:
	  ○ 12 weeks in semen,
	  ○ 8 weeks in urine,
	  ○ 52 weeks in saliva, and
	  ○ 131 weeks in stool.
	• All patients achieved first of 3 consecutive measurements below the lower limit of quantification in semen by 36 week for vector DNA.
	• Magnitude and duration of shedding independent of attained factor VIII activity.

Immunogenicity	• All patients seroconverted to anti-AAV5 antibody positive within 8 weeks. • Titers peaked by 36 weeks. • Cellular immune response to AAV5 capsid peaked at week 2 (70%) and declined at week 26 (23%) and week 52 (17%).
Half-Life	Not applicable
Metabolism	Not applicable

Table 2. Comparative Evidence Table.[1,2]

Ref./ Study Design	Gene Therapy/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mahlangu et al. Ozelo et al. GENEr8-1 study NCT03370913 OL, SA, MC, Phase 3	1. Valoctocogene roxaparvovec-rvox $6x10^{13}$ vector genomes per kg as a single infusion Glucocorticoids (prednisone 60 mg daily tapered over minimum of 8 weeks) or other IS in response to ALT elevations Factor VIII prophylaxis continued x 4 wk then PRN	Demographics: -Mean age 31.7 years -Male 100% -White 71.6% -Asian 14.2% -Black 11.2% -Hispanic/Latino 5.2% -Hepatitis B 14.9% -Hepatitis C 30.6% -HIV 1.5% -0 Problem joints 72.4% -1 Problem joint 12.7% -Baseline bleeding and factor used data 9.2 mo Key Inclusion Criteria: -Men 18 years and older -Severe hemophilia A (factor VIII activity level < 1 IU/dL) -Regular exogenous factor VIII prophylaxis for at least 1 year -No history of Factor VIII inhibitors Key Exclusion Criteria: -Anti-AAV5 capsid antibodies -Significant liver dysfunction or fibrosis; cirrhosis -HIV (added after protocol amendment) -Willing to abstain from alcohol for at least 52 weeks following infusion -Chronic or active hepatitis B	ITT: 134 (all receiving gene therapy) mITT: 132 (ITT & HIV negative) Rollover: 112 (mITT & with at least 6 mo of prospectively collected bleeding and factor VIII usage data from 270-902 study) Attrition: 1 (LTFU at wk 66)	Primary Endpoint: Change from baseline in median factor VIII activity between 49-52 weeks post-treatment (mITT) Baseline: 1 IU/dL Treatment: Median 23.9 IU/dL (IQ, 11.9 to 62.3) Median Change: 22.9 IU/dL (IQ 10.9 to 61.3) Mean±SD: 42.9±45.5 IU/dL Mean Change: 41.9 IU/dL (95% CI 34.1 to 49.7; P<0.001) Median Factor VIII activity post-treatment 40 IU or greater: 37.9 % 5 IU to <40 IU: 50.0% <5 IU: 12.1% (<3 IU: 9.1%; subset of <5 IU) Primary endpoint (2-year extension): Change in annualized bleeding events at week 104 compared to baseline Change -4.1 (95% CI -5.4 to -2.8; P<0.001) Secondary Endpoints (rollover population): Change from baseline in annualized factor VIII concentrate consumption after week 4 Baseline:	NA NA NA	Adverse events: Any event: 100% Grade 3 (overall): 26.1% Grade 3 (ALT increase): 8.2% Grade 4: 0.7% TRAE ≥ 20%: ALT increase: 80.6% AST increase: 29.1% Nausea: 23.1% SAE: Any 16.4% ALT increase: 1.5% Diarrhea: 1.5% Gastroenteritis: 1.5% Rectal hemorrhage: 1.5% Deaths: None Infusion reactions: Systemic hypersensitivity: 5.2% Serious infusion-related reactions: 2.2%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Non-randomized, single arm design. Performance Bias: (Unclear) Open-label before and after study design; Objective measurements for primary outcome, though higher risk of bias for patient reported secondary endpoints of factor VIII use and bleeding events. Detection Bias: (Unclear) Objective measurements for primary outcome of activity level, though higher risk of bias for patient reported secondary endpoints of factor VIII use and bleeding events. Attrition Bias: (Unclear) Low overall attrition. Missing data imputed as LOCF for primary endpoint. Missing values for secondary endpoints imputed as zero. Reporting Bias: (Low) Protocol and study amendments available online. Other Bias: (Unclear) Study designed by sponsor with input from authors (some authors are employees of sponsor). Data collection and analysis performed by employees of the sponsor. First draft written by medical writer contracted by sponsor. Data-access plan was in place to minimize bias by limiting sponsor access to efficacy data before protocol-specified analyses were conducted. **Applicability**: Patient: Similar to disease population. Efficacy and safety in people with liver dysfunction or risk factors is unknown. Intervention: Dose based on phase 1/2 research. Comparator: Single-arm before/after design using prospectively gathered baseline data for most patients. No side by side comparison to existing standard of care or information on lifestyle/activity

		-Active hepatitis C or on antiviral therapy		Mean 3961.2±1751.5 IU/kg/yr Treatment: Mean 56.9 IU/kg/yr (98.6% reduction; P<0.001) Change from baseline in annualized number of treated bleeding events after week 4 Baseline: Mean 4.8±6.5 bleed/yr Treatment: 0.8 bleed/yr Change -4.1 (95% CI, -5.3 to -2.8; P<0.001)	NA			changes or differences between two time periods. Outcomes: Long-term durability unknown. Impact on quality of life was not evaluated. Setting: 48 sites in 13 countries worldwide, 15 US sites
Abbreviations: AAV5 = adeno-associated virus 5; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = Aspartate aminotransferase; CI = confidence interval; dL = deciliter; HIV = human immunodeficiency virus; IQ = interquartile; IS = immunosuppressants; ITT = intention to treat; IU = international unit; kg = kilogram; LOCF = last observation carried forward; LTFU = lost to follow up; MC = multi-center; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PP = per protocol; PRN = as needed; SA = single arm; SD = standard deviation; TRAE = treatment-related adverse event; wk = week.								

References:

1. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. *N Engl J Med.* 2023;388(8):694-705.
2. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *N Engl J Med.* 2022;386(11):1013-1025.
3. Lindsey W, Alexander C, Yang H, Grabowsky A. Gene therapies for hemophilia A and B. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2023.
4. DynaMed. Hemophilia A. EBSCO Information Services. Accessed August 13, 2023. Available at: https://www.dynamed.com/condition/hemophilia-a.
5. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia. 2015;21(5):578-584.
6. Roctavian (valoctocogene roxaparvovec-rvox) prescribing information. Biomarin Pharmaceuticals. June 2023. Available at: https://www.fda.gov/media/169937/download.
7. Long BR, Veron P, Kuranda K, et al. Early Phase Clinical Immunogenicity of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A. *Mol Ther.* 2021;29(2):597-610.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ROCTAVIAN safely and effectively. See full prescribing information for ROCTAVIAN.

ROCTAVIAN (valoctocogene roxaparvovec-rvox) suspension for intravenous infusion
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
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 pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. (1)

----------DOSAGE AND ADMINISTRATION----------
For one-time single-dose intravenous use only. (2)
- Perform baseline testing to select patients, including testing for pre-existing antibodies to adeno-associated virus serotype 5 (AAV5), factor VIII inhibitor presence, and liver health assessments. (2)
- The recommended dose of ROCTAVIAN is 6×10^{13} vector genomes (vg) per kg of body weight. (2.1)
- Start the infusion at 1 mL/min. If tolerated, the rate may be increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- ROCTAVIAN is a suspension for intravenous infusion. (3)
- ROCTAVIAN has a nominal concentration of 2×10^{13} vg valoctocogene roxaparvovec-rvox per mL, each vial contains an extractable volume of not less than 8 mL (16×10^{13} vg). (3)

----------CONTRAINDICATIONS----------
- Active infections, either acute or uncontrolled chronic. (4)
- Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis. (4)
- Known hypersensitivity to mannitol. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion-related reactions: Infusion reactions, including hypersensitivity reactions and anaphylaxis, have occurred. Monitor during and for at least 3 hours after ROCTAVIAN administration. If symptoms occur, slow or interrupt administration and give appropriate treatment. Restart infusion at slower rate once symptoms resolve. Discontinue infusion for anaphylaxis. (2.3, 5.1)
- Hepatotoxicity: Monitor alanine aminotransferase (ALT) weekly for at least 26 weeks 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. Monitor for and manage adverse reactions from corticosteroid use. (5.2)
- Thromboembolic events: Thromboembolic events may occur in the setting of elevated factor VIII activity above the upper limit of normal (ULN). Factor VIII activity above ULN has been reported following ROCTAVIAN infusion. Evaluate for risk factors for thrombosis including cardiovascular risk factors prior to and after ROCTAVIAN use and advise patients accordingly. (5.3)
- Monitoring laboratory tests: Monitor for factor VIII activity and factor VIII inhibitors. (5.4)
- Malignancy: Monitor for hepatocellular malignancy in patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, advanced age). Perform regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing following administration. In the event that any malignancy occurs after treatment with ROCTAVIAN, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100. (5.5)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (incidence ≥ 5%) were nausea, fatigue, headache, infusion-related reactions, vomiting, and abdominal pain. (6)
- Most common laboratory abnormalities (incidence ≥ 10%) were ALT, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), factor VIII activity levels, gamma-glutamyl transferase (GGT) and bilirubin > ULN. (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- For 6 months after administration, men must not donate semen, and men and their female partners must prevent or postpone pregnancy. (8.3)
- There is limited information on the safety and effectiveness of ROCTAVIAN in patients with HIV infection. (8.6)
- The safety and effectiveness of ROCTAVIAN in patients with prior or active factor VIII inhibitors have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2023

Valoctocogene roxaparvovec-rvox

Goal(s):

- Approve valoctocogene roxaparvovec-rvox (ROCTAVIAN) for conditions supported by evidence of benefit.

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Valoctocogene roxaparvovec (billed as pharmacy or physician administered claim)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is it the FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation that the patient has never received another gene therapy for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have severe Hemophilia A with factor VIII activity of < 1 IU/dL?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation that the patient does not have factor VIII inhibitors?	**Yes:** Go to #6 Test date_____ Result_____	**No**: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient 18 years or older?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient tested negative for adeno-associated virus serotype 5 (AAV5) antibodies as measured by an FDA approved test?	**Yes**: Go to #8 Test date_____ Result_____	**No:** Pass to RPh. Deny; medical appropriateness
8. Has this patient had a liver health assessment (ALT, AST, bilirubin, alkaline phosphatase, INR, ultrasound or other radiologic assessment) and were all hepatic enzymes and hepatic radiological tests normal? Note: Mild enzyme elevations which are transient and resolved on repeat testing may answer "Yes" to this question.	**Yes**: Go to # 11	**No:** Go to #9
9. Does the patient have a history of severe liver fibrosis or cirrhosis?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Has the patient been evaluated and cleared for gene therapy treatment by a gastroenterologist or hepatologist?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient able and willing to abstain from alcohol for one year following receipt of gene therapy?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is there documentation that the patient does not have any active, acute or chronic infections, including HIV, hepatitis B, or hepatitis C?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is it anticipated that the patient will be able to safely use corticosteroids or other immunosuppressants for at least 8 weeks if needed?	**Yes**: Approve one lifetime does.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/23 (SF)
Implementation: 11/1/23