MOUNT SINAI HOSPITAL
POLICY & PROCEDURE

POLICY TITLE:	**Etranacogene dezaparvovec-drlb (HEMGENIX) Administration and Clinical Guidelines at Mount Sinai Hospital**		
POLICY NUMBER:	C1.V1	**POLICY OWNER:**	Hemophilia Treatment Center
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I. PURPOSE

This document serves as best practice guideline for the evaluation of patients eligible to receive gene therapy for Hemophilia B, specifically etranacogene dezaparvovec-drlb (HEMGENIX), drug administration, and post administration follow up requirements

II. POLICY

HEMGENIX is the first FDA-approved, one-time gene therapy for the treatment of adults with hemophilia B who currently use Factor IX prophylaxis therapy, have current or historical life-threatening bleeding, or have repeated, spontaneous severe bleeding episodes. Single intravenous (IV) infusion of HEMGENIX results in cell transduction and an increase in circulating factor IX (FIX) activity. Due to the strict drug eligibility and required post-administration follow-ups for close monitoring, establishing and adhering to the institutional best practice guidelines is essential for patient safety.

III. SCOPE

Adherence to this policy applies to all members of the Mount Sinai Health System workforce including, but not limited to: employees, medical staff, volunteers, students, and other persons performing work for or at the Mount Sinai Health System.

IV. DEFINITIONS (OR ATTACHMENTS)

Hemophilia B: Hemophilia B is an X-linked deficiency of coagulation FIX production that results in a lifelong bleeding disorder. The cornerstone of Hemophilia B treatment is replacement of the missing factor via an IV infusion of FIX product prophylactically and/or on-demand for bleeding episodes.

FIX inhibitor: Inhibitors are IgG alloantibodies to exogenous clotting factor that neutralize the function of infused clotting factor concentrates.

V. PROCEDURE

A. PATIENT ELIGIBILITY

1. All patients identified by any provider of care to be potentially eligible to receive HEMGENIX should be referred to the Mount Sinai Hemophilia Treatment Center (HTC) for formal evaluation
2. FIX and FIX inhibitor levels from an outside facility (including network Mount Sinai Locations, Labcorp, Quest Diagnostics, etc.) are not acceptable, but can be used to

screen for eligible patients. All factor levels and inhibitor testing must be performed by the Mount Sinai Hospital Clinical Laboratory located at the main Mount Sinai Hospital campus

3. Potentially eligible patients must:
    a. Be a male greater than 18 years of age
    b. Currently use FIX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes
    c. Have a negative FIX inhibitor titer
        1) If patient is found to have a positive inhibitor, perform a re-test within two weeks
        2) If both initial test and re-test is positive, patient is not eligible for HEMGENIX
    d. Be without evidence of advanced hepatic impairment, including cirrhosis, advanced liver fibrosis (as demonstrated by radiological liver abnormalities), or uncontrolled/active Hepatitis B and C, sustained liver enzymes, and/or viral serology results evaluated by a hepatologist and deemed exclusionary
        1) See section A.4 for specific testing requirements
    e. Be without severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic or cardiovascular disease, or alcoholism
    f. Not have an allergy/anaphylaxis history to any components of HEMGENIX
    g. Not have previous gene therapy treatment
    h. Be deemed able to provide informed signed consent and comply with all aspects of the process
    i. Additional lab tests and/or imaging may be required by the patient's insurance
4. Evaluation of liver health
    a. At minimum, all potential candidates require a liver health assessment consisting of liver enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), as well as hepatic ultrasound and elastography
    b. In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consider a consultation with hepatologist to assess eligibility
    c. All patients from the Mount Sinai HTC will be evaluated by the Institute for Liver Medicine at Mount Sinai Hospital prior to infusion. Their findings and clearance for infusion will be documented in the patient's medical record
5. Antibodies
    a. The presence of preexisting neutralizing anti-AAV antibodies (NAbs) may impede transgene expression
    b. The patient's blood will be sent to Precision for Medicine for testing to determine the presence of pretreatment NAbs
        1) This testing is not licensed by the FDA and is meant for informational purposes to assist in clinical decision-making
    c. Patients with high-titer NAbs may be deemed ineligible for HEMGENIX by the HTC
        1) There is no official cutoff value. Test results will be reviewed and approved on an individual basis
6. Counseling and lifestyle considerations
    a. Given the potential impact of HEMGENIX on liver health, the patient must agree to abstain from alcohol use for at least six months post-infusion
    b. Protected sex and potential impact on male and female fertility
        1) Clinical study post-infusion found that vector DNA was cleared from semen by month 24 in two subjects
        2) The effect of HEMGENIX on fertility in humans has not been studied and is therefore unknown
        3) Would recommend that patient abstain from unprotected sex for at least

one year after administration

c. Vector DNA is widely distributed throughout the body and recipients of HEMGENIX should not donate blood, organs, tissues, or cells for transplantation
d. Given that HEMGENIX is weight-based, advise patient to maintain current weight until after administration of HEMGENIX
e. Patient will need to have an adult over the age of 18 years of age present during the infusion and remain with them in the New York City area for the initial 24 hours after discharge
f. The purchase order is completed by the HTC after insurance authorization has been obtained, and the patient is scheduled for infusion approximately two weeks later
    1) Processing and shipping can take up to two weeks

B. HEMGENIX ORDERING AND ADMINISTRATION

1. An HTC provider orders the HEMGENIX treatment plan within Epic. The treatment plan is co-signed by the HTC MD if the order is placed by the NP (this is a hard stop in Epic).
2. An HTC provider orders steroids before treatment day to have on-hand in case of transaminitis
    a. See section C.5 regarding the management of transaminitis.
3. Prior to administering the product:
    a. Confirm that patient has the steroid prescription on-hand and future lab appointments have been scheduled prior to discharge
    b. Place peripheral IV access
    c. Refer to Pharmacy for full reconstitution procedures
    d. Pre-medicate as ordered in the treatment plan

During administration

    e. Infusion-related reactions may occur:
        1) Symptoms may include chest tightness, headaches, abdominal pain, lightheadedness, flulike symptoms, shivering, flushing, rash, and hypertension
        2) Closely monitor patients for signs or symptoms of an infusion reaction throughout the infusion and for at least three hours after the infusion
        3) If symptoms occur, slow or interrupt the administration of HEMGENIX:
            a. The rate of infusion is 500mL/hr, but can be reduced to 250mL/hr or stopped in the event of a suspected infusion-related reaction
            b. If the infusion is stopped, restart at a slower rate than when the infusion reaction is resolved
            c. If the infusion rate needs to be reduced, or stopped and restarted, HEMGENIX should be infused within 24 hours after the dose preparation
        4) Follow relevant Therapeutic Infusion Center emergency procedures/guidelines

C. POST-INFUSION MONITORING AND FOLLOW-UP

1. The patient and caregiver must remain in New York City for the initial 24 hours post-infusion in case of any delayed post-infusion reactions and should be directed to the Mount Sinai Hospital emergency room for treatment, if patient condition allows. Otherwise, patient should go to the nearest emergency room for evaluation and treatment. In either case, the HTC should be notified of admission requirement.
2. Vector DNA is unlikely to represent infectious particles (the vector is non-pathogenic and cannot replicate), therefore, the risk to third parties (family, healthcare personnel, etc.) can be considered negligible and no specific containment or protection measures are required
3. Frequent lab monitoring post-infusion is necessary to assess the response to gene therapy and any potential immune-related hepatotoxicity, manifesting as asymptomatic

transaminitis, which could result in the loss of FIX gene expression without prompt treatment
    a. Monitor ALT and AST once per week for three months, then once per month for months 4-12 after injection
        1) See section C.5 regarding the management of transaminitis
    b. Monitor FIX activity once per week for three months, then at the discretion of the healthcare provider
    c. Monitor FIX inhibitor levels if patient experiences an increase in bleeding frequency, FIX levels drop unexpectedly, and/or if patient does not respond as expected to FIX infusions
4. In patients with risk factors for hepatocellular carcinoma, monitor Alpha-fetoprotein (AFP) levels and abdominal ultrasound annually
    a. Consider consultation with a hepatologist
    b. Mount Sinai HTC patients will be followed by the Institute for Liver Medicine at Mount Sinai Hospital
5. Management of transaminitis
    a. Most elevations were observed in the first four months after administration
    b. In the event of ALT increase to above normal limits or to twice the patient's baseline in the first three months post-dose, consider initiating a course of corticosteroids
    c. The recommended starting dose is 60mg/day of oral prednisone or prednisolone, with a subsequent taper in response to normalization of the ALT levels (see below)

Timeline	Prednisolone oral dose (mg/day)
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance dose until ALT returns to baseline level	20
Taper after baseline level has been reached	Reduce daily dose by 5 mg/week

    d. The mean duration of corticosteroid use was 81.4 days (standard deviation 28.6) and ranged from 51 to 130 days
6. Continuation of FIX infusion therapy
    a. Patients may continue their routine FIX prophylaxis doses in the first few weeks after the infusion
    b. Discontinue FIX prophylaxis infusions when the patient's endogenous FIX level is ≥ 5%
    c. Consider restarting FIX prophylaxis if FIX is 2-5% in at least two consecutive measurements
    d. Restart FIX prophylaxis if FIX < 2%
    e. On-demand/intermittent FIX doses may be given if the provider deems it necessary

VI. REFERENCES

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Version 1	01/16/24	Original