NEW DRUG APPROVAL

Brand Name	Vivimusta™
Generic Name	bendamustine hydrochloride injection
Drug Manufacturer	Slayback Pharma LLC

New Drug Approval

FDA approval date: December 07, 2022

Review designation: Standard

Type of review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 212209

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Chronic lymphocytic leukemia (CLL)
It is the most common leukemia in adults. It's a type of cancer that starts in cells that become certain white blood cells (called lymphocytes) in the bone marrow. The cancer (leukemia) cells start in the bone marrow but then go into the blood.
In CLL, the leukemia cells often build up slowly. Many people don't have any symptoms for at least a few years. But over time, the cells grow and spread to other parts of the body, including the lymph nodes, liver, and spleen.
he American Cancer Society's estimates for leukemia in the United States for 2022 are:

- About 60,650 new cases of leukemia and about 24,000 deaths from leukemia (all kinds)
- About 20,160 new cases of chronic lymphocytic leukemia (CLL)
- About 4,410 deaths from CLL

CLL accounts for about one-quarter of the new cases of leukemia. The average person's lifetime risk of getting CLL is about 1 in 175 (0.57%). The risk is slightly higher in men than in women.

CLL mainly affects older adults. The average age of people when they are diagnosed is around 70 years. It's rarely seen in people under age 40 and is extremely rare in children.

Non-Hodgkin lymphoma
Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in white blood cells called *lymphocytes*, which are part of the body's immune system. (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in white blood cells called *lymphocytes*, which are part of the body's immune system.

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. The American Cancer Society's estimates for non-Hodgkin lymphoma in 2022 are:

- About 80,470 people (44,120 males and 36,350 females) will be diagnosed with NHL. This includes both adults and children.
- About 20,250 people will die from this cancer (11,700males and 8,550 females).

Overall, the chance that a man will develop NHL in his lifetime is about 1 in 42; for a woman, the risk is about 1 in 52

Efficacy

Chronic Lymphocytic Leukemia (CLL)

The efficacy of bendamustine hydrochloride was evaluated in an open label, randomized, controlled multicenter trial comparing bendamustine hydrochloride to chlorambucil. The trial was conducted in 301 previously untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study. Patients were randomly assigned to receive either bendamustine hydrochloride 100 mg/m2 intravenously over 30 minutes on Days 1 and 2 of each 28-day cycle or chlorambucil 0.8 mg/kg (Broca's normal weight) orally on Days 1 and 15 of each 28-day cycle. The patient populations in the bendamustine hydrochloride and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), sex (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7 x 109 /L vs. 65.1 x 109 /L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL. The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for bendamustine hydrochloride compared to chlorambucil (see Table 1). Survival data are not mature.

Table 1: Efficacy Data for CLL

	Bendamustine Hydrochloride (N=153)	Chlorambucil (N=148)	p-value
Response Rate n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR) †	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4 x 109/L, neutrophils ≥ 1.5 x 109/L, platelets >100 x 109/L, hemoglobin >110 g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

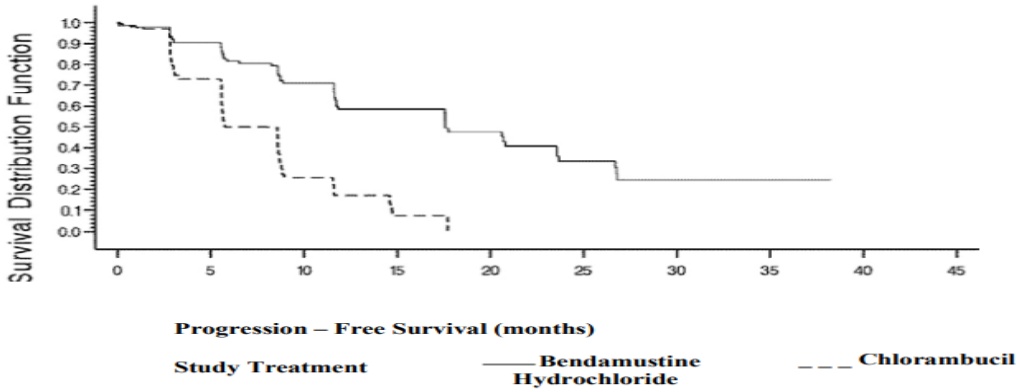
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥50% decrease in peripheral lymphocyte count from the pre-treatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 109/L or 50% improvement over baseline, platelets >100 x 109/L or 50% improvement over baseline, hemoglobin >110 g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

†† PFS was defined as time from randomization to progression or death from any cause.

Kaplan-Meier estimates of progression-free survival comparing bendamustine hydrochloride with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



Non-Hodgkin Lymphoma (NHL)

The efficacy of bendamustine hydrochloride was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received bendamustine hydrochloride 120 mg/m2 intravenously on Days 1 and 2 of a 21-day treatment cycle for up to 8 cycles. The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 2.

Table 2: Efficacy Data for NHL*

	Bendamustine Hydrochloride (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64.3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57

Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval

*IRC assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

- Adverse reactions (> 5%) during infusion and within 24 hours post-infusion are nausea, and fatigue
- Most common adverse reactions(≥15%) for CLL are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, hyperbilirubinemia, pyrexia, nausea, vomiting.
- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia neutropenia, thrombocytopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased dyspnea, rash, and stomatitis.

Safety

ADVERSE EVENTS

The most frequent adverse reactions leading to study withdrawal for patients receiving bendamustine hydrochloride were hypersensitivity (2%) and pyrexia (1%).

Table 3 summarizes the adverse reactions that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Table 3: Non-Hematologic Adverse Reactions that Occurred in at Least 5% of Patients Who Received bendamustine Hydrochloride or Chlorambucil in the Randomized CLL Clinical Study

Adverse Reaction	Bendamustine Hydrochloride (N=153)		Chlorambucil (N=143)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Total number of patients with at least 1 adverse reaction	**121 (79)**	**52 (34)**	**96 (67)**	**25 (17)**
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0

Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

Hematology laboratory abnormalities are described in Table 3. Red blood cell transfusions were administered to 20% of patients receiving bendamustine hydrochloride compared with 6% of patients receiving chlorambucil. Bilirubin elevation occurred in 34% of patients, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively.

Patients treated with bendamustine hydrochloride may also have changes in their creatinine levels.

Table 4: Hematology Laboratory Abnormalities in Patients Who Received bendamustine Hydrochloride or Chlorambucil in the Randomized CLL Clinical Study

Laboratory Abnormality	Bendamustine Hydrochloride (N=150)		Chlorambucil (N=141)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)

Non-Hodgkin Lymphoma (NHL)

Serious adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion-related reactions, Adverse reactions occurring less frequently but possibly related to bendamustine hydrochloride treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

Table 5: Non-Hematologic Adverse Reactions that Occurred in at Least 5% of Patients who Received bendamustine Hydrochloride in the NHL Studies		
Adverse Reaction	**Bendamustine Hydrochloride (N=176*)**	
	All Grades n (%)	**Grade 3 or 4 n (%)**
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac Disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0

Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
Psychiatric disorder		
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3 (2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

***Patients may have reported more than 1 adverse reaction.**
NOTE: Patients counted only once in each preferred term category and once in each body system category.

Hematologic toxicities, based on laboratory values and CTC grade, in patients with NHL treated in both single arm studies combined are described in Table 5. Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in patients with NHL who were treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

Table 6: Hematology Laboratory Abnormalities in Patients Who Received bendamustine Hydrochloride in the NHL Studies		
Hematology Variable	**Bendamustine Hydrochloride**	
	All Grades (%)	**Grade 3 or 4 (%)**
Lymphocytes Decreased	99	94
Leukocytes Decreased	94	56
Hemoglobin Decreased	88	11
Neutrophils Decreased	86	60
Platelets Decreased	86	25

WARNINGS & PRECAUTIONS

Myelosuppression

Vivimusta™ causes myelosuppression. Bendamustine hydrochloride caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia and pneumonia from an opportunistic infection (CMV).

Monitor complete blood counts, including leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Delay the next cycle of therapy if ANC less than 1 x 109 /L or platelet count less than 75 x 109 /L.

Infections

Infection, including pneumonia, sepsis, septic shock, hepatitis and death has occurred in adult and pediatric patients in clinical trials and in post marketing reports for bendamustine hydrochloride. Patients with myelosuppression following treatment with bendamustine hydrochloride are more susceptible to infections. Advise patients with myelosuppression following Vivimusta™ treatment to contact healthcare provider immediately if they have symptoms or signs of infection. Patients treated with Vivimusta™ are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Implement appropriate measures (including clinical and laboratory monitoring, prophylaxis, and treatment) for infection and infection reactivation prior to administration.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML), including fatal cases, have occurred following treatment with bendamustine, primarily in combination with rituximab or Obinutuzumab. Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected, withhold Vivimusta™ treatment and perform appropriate diagnostic evaluations. Consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Anaphylaxis and Infusion-Related Reactions

Infusion-related reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion-related reactions after their first cycle of

therapy. Do not rechallenge patients who experienced Grade 3 or worse allergic-type reactions. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion-related reactions. Discontinue Vivimusta™ for patients with Grade 4 infusion-related reactions. Consider discontinuation for Grade 3 infusion-related reactions as clinically appropriate considering individual benefits, risks, and supportive care.

Tumor Lysis Syndrome

Tumor lysis syndrome associated with bendamustine hydrochloride has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Administer vigorous hydration and monitor blood chemistry, particularly potassium and uric acid levels, at baseline and closely during treatment with Vivimusta™. Allopurinol has also been used during the beginning of bendamustine hydrochloride therapy. However, there may be an increased risk of severe skin toxicity when bendamustine hydrochloride and allopurinol are administered concomitantly.

Skin Reactions

Fatal and serious skin reactions have been reported with bendamustine hydrochloride treatment in clinical trials and postmarketing safety reports, including toxic skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash. Events occurred when bendamustine hydrochloride was given as a single agent and in combination with other anticancer agents or allopurinol. Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue Vivimusta™.

Hepatotoxicity

Fatal and serious cases of liver injury have been reported with Bendamustine Hydrochloride Injection. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients. Most cases were reported within the first three months of starting therapy. Monitor liver chemistry tests prior to and during treatment with Vivimusta™.

Other Malignancies

Pre-malignant and malignant diseases have developed in patients who have been treated with bendamustine hydrochloride, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, bronchial carcinoma, and non-melanoma skin cancer including basal cell carcinoma and squamous cell carcinoma.Monitor patients for the development of secondary malignancies. Perform dermatologic evaluations during and after treatment with Vivimusta™.

Extravasation Injury

Bendamustine hydrochloride extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting Vivimusta™ infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of Vivimusta™.

Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and the drug's mechanism of action, Vivimusta™ can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine (that approximated the maximum recommended human dose based on body surface area) to pregnant mice and rats during organogenesis caused adverse developmental outcomes, including an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with

Vivimusta™ and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Vivimusta™ and for 3 months after the last dose.

CONTRAINDICATIONS

Vivimusta is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, dehydrated alcohol, or monothioglycerol.

Clinical Pharmacology

MECHANISMS OF ACTION

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

Dose & Administration

ADULTS

For CLL:

- 100 mg/m2 infused intravenously over 20 minutes on Days 1 and 2 of a 28- day cycle, up to 6 cycles.

For NHL:

- 120 mg/m2 infused intravenously over 20 minutes on Days 1 and 2 of a 21- day cycle, up to 8 cycles.

PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Do not use Vivimusta™ in patients with creatinine clearance (CLcr) less than 30 mL/min.

HEPATIC IMPAIRMENT

Do not use Vivimusta™ in patients with AST or ALT 2.5 to 10 times upper limit of normal (ULN) and total bilirubin 1.5 to 3 times ULN or total bilirubin greater than 3 times ULN.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow solution in multiple-dose vial.