HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HEPZATO safely and effectively. See full prescribing information and HEPZATO KIT Hepatic Delivery System Instructions for Use.

HEPZATO (melphalan) for injection is a component of the HEPZATO KIT Hepatic Delivery System (HDS) for intra-arterial use. Initial U.S. Approval: 1964

WARNING: SEVERE PERI-PROCEDURAL COMPLICATIONS, MYELOSUPPRESSION

See full prescribing information for complete boxed warning.

- **Severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events may occur with intra-hepatic administration of HEPZATO. Assess patients for these adverse reactions during and for 72 hours following administration of HEPZATO. (5.1)**
- **HEPZATO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy called the HEPZATO KIT REMS. (5.2)**
- **Myelosuppression with resulting severe infection, bleeding, or symptomatic anemia may occur with HEPZATO. Monitor hematologic laboratory parameters and delay additional cycles of HEPZATO therapy until blood counts have improved. (5.3)**

INDICATIONS AND USAGE

HEPZATO is an alkylating drug indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.(1)

DOSAGE AND ADMINISTRATION

HEPZATO, a component of the HEPZATO KIT, is administered by intra-arterial infusion into the hepatic artery (see instructions for use [IFU]). The recommended dose is 3 mg/kg based on ideal body weight (see Table 1), with a maximum absolute dose of 220 mg during a single HEPZATO treatment. (2.2). The drug is infused over 30 minutes followed by a 30-minute washout period (see IFU). Treatments should be administered every six (6) to eight (8) weeks but can be delayed until recovery from toxicities and as per clinical judgement. (2.3)

DOSAGE FORMS AND STRENGTHS

For injection: HEPZATO includes 50 mg freeze-dried (lyophilized) melphalan powder per vial in five (5) single dose vials, intended for reconstitution with the supplied diluents. (3)

CONTRAINDICATIONS

- Active intracranial metastases or brain lesions with a propensity to bleed
- Liver failure, portal hypertension, or known varices at risk for bleeding
- Surgery or medical treatment of the liver in the previous 4 weeks
- Active cardiac conditions including, but not limited to, unstable coronary syndromes (unstable or severe angina or myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias, or severe valvular disease
- History of allergies or known hypersensitivity to melphalan or a component or material utilized within the HEPZATO KIT including natural rubber latex, heparin, and severe hypersensitivity to iodinated contrast not controlled by antihistamines and steroids (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, have occurred in patients who received an intravenous (IV) formulation of melphalan. Immediately terminate hepatic arterial melphalan infusion for hypersensitivity reactions and administer supportive care. **(5.4)**
- Gastrointestinal disturbances such as nausea and vomiting, abdominal pain and diarrhea are common. (5.5)
- Carcinogenic/Mutagenic effects: Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating drugs (including melphalan). Melphalan has been shown to cause chromatid or chromosome damage in humans. (5.6)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)
- Infertility: Melphalan-based chemotherapy regimens have been reported to cause suppression of ovarian function in premenopausal women and testicular suppression in men. (5.8)

ADVERSE REACTIONS

Most common (≥20%) adverse reactions or laboratory abnormalities are thrombocytopenia, fatigue, anemia, nausea, musculoskeletal pain, leukopenia, abdominal pain, neutropenia, vomiting, increased alanine aminotransferase, prolonged activated partial thromboplastin time, increased aspartate aminotransferase, increased alkaline phosphatase, and dyspnea.

To report SUSPECTED ADVERSE REACTIONS, contact Delcath at 1-833-632-0458 **and www.Delcath.com or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.**

USE IN SPECIFIC POPULATIONS

- HEPZATO should not be used in patients < 35 kg. (2.2)
- Lactation: Advise not to breastfeed (8.2)

See 17 PATIENT COUNSELING INFORMATION

Revised: 8/2023

FULL PRESCRIBING INFORMATION: *CONTENTS
WARNING: PERI-PROCEDURAL COMPLICATIONS, BONE MARROW SUPPRESSION
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***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: PERI-PROCEDURAL COMPLICATIONS, MYELOSUPPRESSION

- **Severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events may occur via hepatic intra-arterial administration of HEPZATO. Assess patients for these adverse reactions during and for at least 72 hours following administration of HEPZATO *[see Warnings and Precautions (5.1)].***
- **HEPZATO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy called the HEPZATO KIT REMS *[see Warnings and Precautions (5.2)].***
- **Myelosuppression with resulting severe infection, bleeding, or symptomatic anemia may occur with HEPZATO. Monitor hematologic laboratory parameters and delay additional cycles of HEPZATO therapy until blood counts have improved. *[see Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

HEPZATO for injection, as a component of the HEPZATO KIT, is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.

2 DOSAGE AND ADMINISTRATION

2.1 Important Pre-Treatment and Administration Information

HEPZATO is a component of the HEPZATO KIT Hepatic Delivery System [HDS]. Refer to the HEPZATO KIT Hepatic Delivery System Instructions for Use (IFU) for additional instructions including pre-infusion evaluation, hydration, premedication, anticoagulation, and supportive care.

Caution: The double balloon catheter component of the HDS contains natural rubber latex which may cause allergic reactions *[see Contraindications (4)]*.

- Healthcare providers must complete the required HEPZATO KIT REMS training prior to administration of the HEPZATO KIT *[see Warnings and Precautions (5.2)]*.
- Discontinue oral anticoagulation and drugs affecting platelet function prior to the procedure *[see Warnings and Precautions (5.1)]*.
- Discontinue ACE-inhibitors, calcium channel blockers, or alpha-1-adrenergic blockers prior to the procedure *[see Warnings and Precautions (5.1)]*.
- Conduct baseline hematologic testing. Administer intra-hepatic HEPZATO with the HEPZATO KIT only to patients with the following *[see Warnings and Precautions (5.3)]*.
    - Hemoglobin ≥ 10 g/dL
    - Platelets ≥ 100,000/microliter
    - Neutrophils > 2000/microliter

2.2 Recommended Dosage

- Administer HEPZATO via the HEPZATO KIT Hepatic Delivery System only to patients weighing 35 kg or greater due to potential size limitations with respect to percutaneous catheterization.
- HEPZATO, a component of the HEPZATO KIT, is administered by infusion into the hepatic artery (see IFU) every 6 to 8 weeks for up to 6 total infusions.
- The recommended HEPZATO dose is 3 mg/kg based on ideal body weight (IBW), as calculated per Table 1 below, with a maximum of 220 mg during a single treatment.

Table 1: Calculation of IBW for HEPZATO Dosing

	Height	**Ideal Body Weight**
Men	≥ 152 cm	52 kg + (0.75 kg/cm of height greater than 152 cm)
	< 152 cm	52 kg – (0.75 kg/cm of height less than 152 cm)
Women	≥ 152 cm	49 kg + (0.67 kg/cm of height greater than 152 cm)
	< 152 cm	49 kg – (0.67 kg/cm of height less than 152 cm)

2.3 Dosage Modifications for Adverse Reactions

A dosage reduction to 2 mg/kg is recommended for subsequent treatments for the following reasons:

- Grade 4 neutropenia of > 5 days duration despite growth factor support or associated with neutropenic fever;
- Grade 4 thrombocytopenia of > 5 days duration or associated with a hemorrhage that required a transfusion;

HEPZATO administered with the HEPZATO KIT should be discontinued if patients have life threatening or HEPZATO-related persistent toxicity that has not resolved to Grade 2 or less by 8 weeks following treatment.

2.4 Preparation and Administration

Refer to the HEPZATO KIT Hepatic Delivery System IFU for further details and instructions.

Reconstitute and dilute melphalan immediately prior to beginning intra-arterial infusion.

Reconstituted and diluted solutions of HEPZATO are unstable. No more than 60 minutes should elapse from reconstitution and completion of the intra-hepatic infusion of the diluted HEPZATO solution. A citrate derivative of melphalan has been detected in reconstituted HEPZATO in 30 minutes, and nearly 1% of labeled strength of melphalan hydrolyzes every 10 minutes when reconstituted HEPZATO is further diluted in 0.9% Sodium Chloride. A precipitate forms if the reconstituted solution is stored at 5°C. Do not refrigerate HEPZATO once reconstituted.

HEPZATO is a hazardous drug[1]. Follow applicable special handling and disposal procedures.

Reconstitution and Dilution Instructions:

1. Rapidly (in 5 seconds or less) inject 10 mL of the supplied sterile diluent [*see Dosage Forms and Strengths (3.0)*] into the HEPZATO 50 mg vial using a sterile needle (20-gauge or larger) and syringe. The resulting solution will contain melphalan 5 mg/mL
2. Immediately shake the vial vigorously until a clear solution is obtained. No more than five (5) seconds should elapse between the discharge of the syringe and the commencement of shaking.
3. Immediately further dilute the required dose with the provided 0.9% sodium chloride injection, United States Pharmacopeia (USP), to a concentration not greater than 0.45 mg/mL, as follows:
    - HEPZATO doses up to 110 mg:

      Dilute in 250 mL of 0.9% sodium chloride injection
    - HEPZATO doses 111 mg to 220 mg:

      Divide the total dose equally into 2 and dilute each in 250 mL of 0.9% sodium chloride injection (for example, if the total dose is 200 mg, dilute 100 mg in each 250 mL 0.9% sodium chloride injection)
4. Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
5. Administer diluted HEPZATO intra-arterially as described in the IFU. Complete the infusion within 30 minutes, followed by a 30-minute washout period. Refer to the IFU for additional administration procedures.

3 DOSAGE FORMS AND STRENGTHS

HEPZATO (melphalan) is supplied in the HEPZATO KIT that contains the following:

- Melphalan for injection: 5 single dose, clear glass vials for injection, containing 50 mg white to pale yellow lyophilized powder, intended for reconstitution with the supplied diluents

4 CONTRAINDICATIONS

HEPZATO and the HEPZATO KIT are contraindicated in patients with:

- Active intracranial metastases or brain lesions with a propensity to bleed
- Liver failure, portal hypertension, or known varices at risk for bleeding
- Surgery or medical treatment of the liver in the previous 4 weeks
- Uncorrectable coagulopathy
- Inability to safely undergo general anesthesia, including active cardiac conditions including, but not limited to, unstable coronary syndromes (unstable or severe angina or myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias, or severe valvular disease

- History of allergies or known hypersensitivity to melphalan
- History of allergies or known hypersensitivity to a component or material utilized within the HEPZATO KIT including:
    - History of allergy to natural rubber latex
    - History of allergy or hypersensitivity to heparin or presence of heparin-induced thrombocytopenia (HIT)
    - History of severe allergic reaction to iodinated contrast not controlled by premedication with antihistamines and steroids

5 WARNINGS AND PRECAUTIONS

5.1 Peri-Procedural Complications

Hemorrhage, hepatocellular injury, and thromboembolic events have been observed when HEPZATO has been administered via hepatic intra-arterial administration. Administration of HEPZATO requires general anesthesia and extracorporeal bypass of circulation which may cause life threatening or fatal adverse effects. Ensure the patient is euvolemic but do not overhydrate the patient. Monitor for these peri-procedural complications during the procedure and for at least 72 hours following the procedure.

To mitigate the risk of thromboembolic events, administer anticoagulation as described in the IFU during the procedure.

Due to the risk of bleeding, do not use in patients with uncorrectable coagulopathies and delay treatment with the HEPZATO KIT for at least 4 weeks after surgery or other medical procedure involving the liver. Platelets and clotting factors may be removed during the HEPZATO KIT procedure. Monitor platelets and coagulation parameters as described in the IFU. If life-threatening bleeding occurs during the procedure, reverse anticoagulation as described in the IFU and correct coagulopathy as appropriate. Discontinue anticoagulation with warfarin or other oral anticoagulants prior to the procedure; resume when hemostasis has been restored after the procedure, provided no bleeding complications have been observed. Refer to the Prescribing Information of the anticoagulant agent for bridging recommendations for anti-coagulation prior to surgical procedures. Discontinue drugs affecting platelet function such as aspirin, non-steroidal anti-inflammatory drugs, or other anti-platelet drugs one week before the procedure.

Patients with abnormal hepatic vascular (especially arterial supply) or biliary (especially re-implantation of bile duct) anatomy or gastric acid hypersecretion syndromes may be at increased risk of peri-procedural complications or other severe adverse reactions. Screen patients for a history of prior surgeries involving the bile duct to assess whether the patient is an appropriate candidate for HEPZATO KIT and monitor patients for adverse reactions following HEPZATO KIT administration.

Procedure-related reductions in blood pressure including severe hypotension can occur during the HEPZATO KIT procedure. Closely monitor blood pressure during the procedure. Patients may require fluid support and vasopressors. To reduce the risk of severe hypotension, assess hypothalamic-pituitary-adrenal axis function, and temporarily discontinue ACE-inhibitors, calcium channel blockers, or alpha-1-adrenergic blockers for at least 5 half-lives prior to

treatment with the HEPZATO-KIT. If necessary, use other short-acting antihypertensive drugs to manage blood pressure during the peri-procedure period.

5.2 HEPZATO KIT REMS PROGRAM

The HEPZATO KIT is only available through a restricted program under a REMS, because of the risk of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events defined in the REMS. The HEPZATO KIT should only be used by trained healthcare providers *[see Warnings and Precautions (5.1)]*.

Important requirements of the HEPZATO KIT REMS include:

- Healthcare settings that dispense and administer HEPZATO KIT must be enrolled, certified, and comply with the REMS requirements.
- Certified healthcare facilities must ensure that healthcare providers who perform the Percutaneous Hepatic Perfusion (PHP) procedure are trained on the use of HEPZATO KIT and must only dispense HEPZATO when authorized to do so by the REMS.
- Certified healthcare facilities must ensure that patients are assessed for severe peri-procedural complications during the procedure and for at least 72 hours following the procedure.

Further information is available at www.HEPZATOKITREMS.com or contact Delcath Systems at 1-833-632-0457.

5.3 Myelosuppression

Hematologic adverse reactions, including thrombocytopenia, anemia, and neutropenia have been reported in patients treated with HEPZATO. The risk of hematologic adverse reactions may be increased in patients who have received prior chemotherapy, bone irradiation, or who have compromised bone marrow function.

In the 95 patients who received HEPZATO in the FOCUS trial, 68% had Grade 3 or 4 myelosuppression. A total of 55%, 33%, and 30% experienced Grade 3 or 4 thrombocytopenia, anemia, and neutropenia, respectively. Median time to thrombocyte nadir was 13 days (range: 3-33) after treatment with median recovery in 20 days (range: 4-29) after treatment. Median time to hemoglobin nadir was 10 days (range: 3-21) after treatment with median recovery in 13 days (range: 4-28) after treatment. Median time to neutrophil nadir was 11 days (range: 3-36) after treatment with median recovery in 17 days (range: 9-36) after treatment.

Monitor patients for severe infections, bleeding, and symptomatic anemia. Only administer HEPZATO in patients with platelets >100,000/microliter, hemoglobin ≥10.0 gm/dL and neutrophils >2,000/microliter. Administer transfusions or growth factors as appropriate *[see Dosage and Administration (2.1)]*.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received an intravenous (IV) formulation of melphalan. These reactions with melphalan are characterized by urticaria, pruritus, edema, skin rashes, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. Hypersensitivity can occur in patients with or without prior exposure to IV or oral melphalan.

When a hypersensitivity reaction is observed, immediately terminate the hepatic arterial HEPZATO infusion and administer necessary supportive care *[see Contraindications (4)]*.

Patients with a history of allergic reactions to iodinated contrast may experience hypersensitivity reactions, including anaphylaxis, during treatment with the HEPZATO KIT. Premedicate patients with a history of allergic reaction to iodinated contrast prior to treatment with HEPZATO KIT. Do not administer HEPZATO KIT in patients with a history of severe allergic reactions or anaphylaxis to iodinated contrast *[see IFU, see Contraindications (4)]*.

5.5 Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions including nausea and vomiting, abdominal pain, and diarrhea are common, and occurred in 84% of patients treated with HEPZATO in the FOCUS trial. Administer a proton pump inhibitor the day prior to and the morning of the procedure. If anti-emetic treatment is required, pre-medicate with anti-emetic therapy in subsequent cycles.

5.6 Secondary Malignancies

Melphalan has been shown to cause chromatid or chromosome damage in humans. Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with intravenous alkylating drugs including melphalan. Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantification of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received oral or IV melphalan (and other alkylating drugs) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose *[see Nonclinical Toxicology (13.1)]*.

5.7 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, melphalan can cause fetal harm when administered to a pregnant woman. Melphalan is genotoxic, targets actively dividing cells, and was embryolethal and teratogenic in rats. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with HEPZATO and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HEPZATO and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

5.8 Infertility

Melphalan-based chemotherapy regimens have been reported to cause suppression of ovarian function in premenopausal women, resulting in persistent amenorrhea in approximately 9% of patients. Reversible or irreversible testicular suppression has also been reported *[see Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

Below are adverse reactions associated with HEPZATO KIT. Additional adverse reactions related to the procedure and/or medical device are described in further detail in the HEPZATO

KIT IFU. The following clinically significant adverse reactions are described elsewhere in the labeling:

- Peri-procedural complications *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Secondary Malignancies *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

The adverse drug reactions (ADRs) described in this section were identified from the FOCUS trial. FOCUS was a multicenter trial that evaluated HEPZATO (melphalan) administered via the HEPZATO KIT in patients with unresectable hepatic metastases from uveal melanoma. In the FOCUS trial, a total of 95 patients were enrolled into the HEPZATO KIT arm, of which 91 patients received treatment with HEPZATO.

Serious adverse reactions occurred in 45% of patients who received HEPZATO. Serious adverse reactions occurring in ≥ 2% of patients were thrombocytopenia (10%), neutropenia (8%), febrile neutropenia (7%), platelet count decreased (6%), leukopenia (4.2%), cardiac arrest (3.2%), neutrophil count decreased (2.1%), hypoxia (2.1%), pleural effusion (2.1%), pulmonary edema (2.1%), and deep vein thrombosis (2.1%). Fatal adverse reactions occurred in 3 (3.2%) patients who were treated with HEPZATO; these included cardiac arrest, acute hepatic failure and bacterial peritonitis.

HEPZATO was permanently discontinued due to adverse reactions in 18% of patients with neutropenia being the most common adverse reaction (3.2%) requiring permanent discontinuation.

Dose reductions due to an adverse reaction occurred in 14% of patients who received HEPZATO. Adverse reactions which required dose reductions occurring in ≥ 2% of patients were platelet count decreased (6%), neutropenia (4.2%), anemia (2.1%), and thrombocytopenia (2.1%).

Adverse reactions that required dosage interruption in ≥ 2% of patients who received HEPZATO were platelet count decreased (6%), neutropenia (5%), thrombocytopenia (3.2%), anemia (3.2%) and febrile neutropenia (2.1%).

The most common (≥20%) adverse reactions or laboratory abnormalities reported in patients treated with HEPZATO were thrombocytopenia (65%), fatigue (65%), anemia (63%), nausea (57%), musculoskeletal pain (46%), leukopenia (46%), abdominal pain (39%), neutropenia (35%), vomiting (35%), increased alanine aminotransferase (32%), prolonged activated partial thromboplastin time (28%), increased aspartate aminotransferase (28%), increased blood alkaline phosphatase (27%), and dyspnea (23%).

Table 2 and Table 3 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in FOCUS.

Table 2 All Adverse Reactions Observed at a Frequency of >10% in Patients Treated with HEPZATO

	All Adverse Reactions N=95	
	All Grades (%)	**Grades 3 or 4 (%)**
Gastrointestinal disorders		
Nausea	57	0
Abdominal Pain[1]	39	1
Vomiting[1]	35	0
Diarrhea[1]	17	1
General disorders		
Fatigue[1]	65	0
Pyrexia[1]	16	0
Musculoskeletal And Connective Tissue Disorders		
Musculoskeletal Pain[1]	46	1
Groin Pain	11	0
Respiratory disorders		
Dyspnea[1]	23	2
Cough[1]	15	0
Nervous system disorders		
Headache[1]	19	0
Lethargy	12	0
Dizziness[1]	11	0
Injury and procedural complications		
Contusion	17	0
Metabolism and nutrition disorders		
Decreased appetite	16	0
Vascular disorders		
Hemorrhage[1]	15	1
Hypotension[1]	13	3

[1] Represents a composite of multiple, related preferred terms

Table 3: Laboratory Abnormalities Observed at a Frequency of >10% in Patients Treated with HEPZATO

Laboratory Abnormality	All Laboratory Abnormalities N=95	
	All Grades (%)	Grades 3 or 4 (%)
Platelets decreased[a]	65	55
Hemoglobin decreased[a]	63	33
Leukocytes decreased[a]	46	34
Neutrophils decreased[a]	35	30
Alanine aminotransferase increased	32	3
International normalized ratio increased	31	8
Activated partial thromboplastin time prolonged	28	8
Aspartate aminotransferase increased	28	4
Blood alkaline phosphatase increased	27	2
Calcium decreased	13	3
Troponin I increased	13	2
Blood bilirubin increased	11	3

[a] Represents a composite of multiple, related preferred terms

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, melphalan can cause fetal harm when administered to a pregnant woman, including teratogenicity and/or embryo-fetal lethality [see *Clinical Pharmacology (12.1)*]. Melphalan is a genotoxic drug and can cause chromatid or chromosome damage in humans [see *Nonclinical Toxicology (13.1)*]. In animal studies, melphalan was embryolethal and teratogenic in rats at doses below the recommended clinical doses [see Data]. Advise a pregnant woman of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the United States general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Adequate animal studies have not been conducted with IV melphalan. Melphalan was embryolethal and teratogenic in rats following oral administration of 6 to 18 mg/m^2/day for ten (10) days (0.05 to 0.16 times the recommended clinical dose of 3 mg/kg or 111 mg/m^2/day) and intraperitoneal administration of 18 mg/m^2 (0.16 times the highest recommended clinical dose). Malformations resulting from melphalan administration included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, and hepatocele (exomphaly).

8.2 Lactation

Risk Summary

It is not known whether melphalan is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing children from melphalan, breastfeeding is not recommended during treatment with melphalan and for one week after the last dose.

8.3 Females and Males of Reproductive Potential

Melphalan can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating HEPZATO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with HEPZATO and for 6 months after the last dose.

Males

HEPZATO administration may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Advise males with female partners of reproductive potential to use effective contraception during treatment with HEPZATO and for 3 months after the last dose [see *Nonclinical Toxicology (13.1)*].

Infertility

Females

Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients.

Males

Reversible and irreversible testicular suppression has been reported in male patients after administration of melphalan.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of HEPZATO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In the FOCUS trial, 30 of the 91 patients (33%) were 65 years and older.

10 OVERDOSAGE

No information on melphalan overdosage is available following administration of HEPZATO. Overdoses resulting in death have been reported following treatment with high intravenous (IV) doses of melphalan.

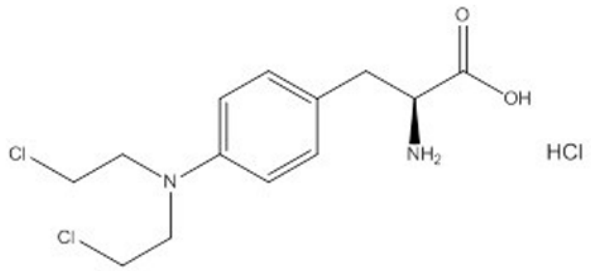
Overdoses via the IV route, including doses up to 290 mg/m^2 (approximately 7.5 mg/kg IBW), have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions, muscular paralysis, and cholinomimetic effects. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage of the gastrointestinal tract occur at high IV doses (>100 mg/m^2 or approximately 2.6 mg/kg IBW). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Significant hyponatremia caused by an associated inappropriate secretion of antidiuretic hormone syndrome has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported.

The principal toxic effect is bone marrow suppression. Hematologic parameters should be closely followed for three (3) to six (6) weeks. General supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the physician. General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalization, antibiotic cover, and the use of hematological growth factors.

This drug is not removed from systemic plasma to any significant degree by hemodialysis or hemoperfusion.

11 DESCRIPTION

Melphalan, is a bifunctional alkylating drug that is active against selected human neoplastic diseases. Melphalan is available as melphalan hydrochloride salt. The chemical name of melphalan hydrochloride is 4-[bis(2-chloroethyl)amino]-L-phenylalanine hydrochloride. The molecular formula is $C_{13}H_{18}Cl_2N_2O_2$.HCl and the molecular weight is 341.67.



Melphalan is practically insoluble in water and has a pKa1 of ~2.5.

HEPZATO, for injection, is supplied as a sterile, nonpyrogenic, freeze-dried white to pale yellow freeze-dried cake/ powder. Each single dose vial contains melphalan 50 mg, equivalent to 56 mg of melphalan hydrochloride and 20 mg povidone.

HEPZATO (melphalan) is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and water for injection to a total of 10 mL.

HEPZATO (melphalan) for use with the hepatic delivery system is administered intra-arterially.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Melphalan is an alkylating drug of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N7 position of guanine. It is active against both resting and rapidly dividing tumor cells.

12.2 Pharmacodynamics

Exposure-Response

Melphalan exposure-response relationships and the time course of pharmacodynamic response following administration of HEPZATO via the Hepatic Delivery System are not fully characterized.

12.3 Pharmacokinetics

Geometric mean of systemic melphalan maximum concentration (C_{max}) is 2.4 (%CV 3.0) mcg/mL and the $AUC_{0\text{-}last}$ was 1.8 (%CV 1.1) mcg*hr/mL.

The melphalan median (range) time to C_{max} (T_{max}) is 0.57 (0.05 – 1.18) hours following administration of HEPZATO.

Distribution

The melphalan plasma protein binding is approximately 78% following administration of HEPZATO. Serum albumin accounts for approximately 40% to 60% and α_1-acid glycoprotein approximately 20% of the plasma protein binding.

Elimination

The median terminal elimination phase half-life of 1.07 hours that is consistent with IV melphalan administration.

Metabolism:

Melphalan is primarily metabolized by hydrolysis to inactive metabolites.

Excretion:

Liver uptake and removal of melphalan by isolation of hepatic venous blood and subsequent filtration by HDS are the two main processes for reducing the amount of melphalan that is available systemically following administration of HEPZATO. HDS reduced systemic melphalan exposure with a mean (SD) filter efficiency of 82.7% (14.4%) for the total filtration period.

Systemic melphalan is eliminated by renal excretion of parent drug and metabolites.

Specific Populations

No clinically significant differences in the pharmacokinetics of melphalan were observed based on body weight (43 - 150 kg), creatinine clearance (> 50 mL/min), or hepatic parameters (ALT (7 - 157 IU/L), AST (11 - 90 IU/L), or bilirubin (0.06 - 1.5 mg/dL) following administration of HEPZATO KIT.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However, intraperitoneal (IP) administration of melphalan in rats (5.4 to 10.8 mg/m^2) and in mice (2.25 to 4.5 mg/m^2) 3 times per week for 6 months followed by 12 months post-dose observation produced peritoneal sarcoma and lung tumors, respectively.

Intramuscular administration of melphalan at 6 and 60 mg/m^2 produced structural aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

14 CLINICAL STUDIES

Study in Patients with Uveal Melanoma

The efficacy of HEPZATO in hepatic-dominant metastatic uveal melanoma was based on the results from 91 patients who received HEPZATO via the HEPZATO KIT in the FOCUS Study (NCT02678572), a multicenter, open-label trial. To be eligible for enrollment, patients were required to have metastatic uveal melanoma with metastases predominately involving the liver (liver dominant). Limited extrahepatic disease in the bone, subcutaneous sites, lymph nodes, or lung was permitted if the life-threatening component of the uveal melanoma was in the liver and the extrahepatic disease was amenable to resection or radiation and had a defined treatment plan. Patients with metastases in more ≥ 50% of the liver parenchyma, unable to undergo general anesthesia, ECOG ≥2, platelets < 100,000/microliter, absolute neutrophil count < 1,500/microliter, hemoglobin < 10 gm/dL, Child-Pugh Class B or C cirrhosis, or hepatitis B or C infection were excluded.

Patients received 3 mg/kg of melphalan based on ideal body weight (IBW, maximum total dose of 220 mg) administered intraarterially using the Hepatic Delivery System (HDS) every 6-8 weeks for up to 6 infusions. The median number of infusions administered per patient was 4 (range: 1-6). Thirty-seven percent (37%) of the 91 patients treated received the maximum of six infusions of treatment.

The major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR) using computed tomography (CT) or magnetic resonance imaging (MRI) assessed by an independent central review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age of patients was 61 years (range 20 to 78), 52% were female, 95% were White, 5% unavailable, and all patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-five percent (95%) of enrolled patients had either 2 or 3 hepatic lesions. Seventy-nine percent (79%) of patients had <25% liver involvement. Thirty percent of the treated patients had extra-hepatic lesions, of which 20% had 1 extrahepatic lesion and 10% had 2

or more; overall 12% of patients had lung, 11% soft tissue/subcutaneous, 5% lymph node, and 4% had bone involvement. Forty-three percent (43%) of patients underwent prior therapy for metastatic disease, including systemic therapy (25%), other surgeries or procedures (14%), and radiation (11%).

The efficacy results of HEPZATO treatment are summarized in Table 4.

Table 4 Efficacy Results for Patients in FOCUS Trial

	HEPZATO (N=91)
Objective Response Rate	
ORR (95% CI)[1]	36.3% (26.4, 47.0)
Complete Response	7.7%
Partial Response	28.6%
Duration of response (months)	
Number of Responders	n= 33
Median[2] (months) (95% CI)[3]	14.0 (8.3, 17.7)
% Responder with DoR≥6 months[4]	70 %
% Responder with DoR≥12 months[4]	30 %

[1] Clopper-Pearson method [2] Kaplan Meier method [3] Brookmeyer and Crowley method [4] Based on observed duration of response

15 REFERENCES

[1]OSHA Hazardous Drugs. OSHA. http://www.osha.gov/hazardous-drugs

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

The HEPZATO KIT includes the HEPZATO 5 x 5 Drug Pack and the Hepatic Delivery System (HDS). Each 5 x 5 HEPZATO KIT Drug Pack includes HEPZATO (melphalan) and diluents for reconstitution and dilution:

- Each vial of HEPZATO contains 50 mg melphalan for injection supplied as a sterile, nonpyrogenic, freeze-dried cake/powder in a carton containing 5 single-dose, glass vials (NDC 75833-800-01).
- Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and water for injection to a total of 10 mL in a carton containing 5 single-dose, glass vials for reconstitution (NDC 75833-700-01).
- Each of two 250 mL plastic containers of 0.9% sodium chloride injection USP (NDC 0264-7800-20).

HEPZATO (melphalan) for injection must only be administered with the HDS device supplied with the HEPZATO KIT and components specified by Delcath Systems, Inc, in the IFU *[see Dosage and Administration (3)]*.

Storage and Handling

HEPZATO for injection and its associated diluents including 0.9% sodium chloride must be stored at controlled room temperature 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted between 15°C- 30°C (59°F-86°F) [see USP Controlled Room Temperature].

The Hepatic Delivery System components may be stored at room temperature.

Melphalan is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

HEPZATO is light sensitive. Retain in original carton until use.

HEPZATO (melphalan) for injection

Manufactured for:
Delcath Systems, Inc.
Queensbury, NY 12804
by Mylan Institutional LLC
Made in Italy

HEPZATO KIT melphalan for Injection/Hepatic Delivery System

Packaged and Distributed by:
Delcath Systems, Inc.
Queensbury, NY 12804

17 PATIENT COUNSELING INFORMATION

Advise patients or their caregivers of the following risks of the HEPZATO KIT:

Peri-Procedural Complications

- Advise patients of the severe procedural risks associated with administration of melphalan using the HEPZATO KIT including hemorrhage, hepatic injury and thromboembolic events.
- Advise patients that they will be monitored in a hospital setting following each treatment.
- Advise patients taking anti-coagulant and anti-hypertensive medications that these may need to be discontinued prior to treatment with HEPZATO KIT *[see Warnings and Precautions (5.1)]*.

Myelosuppression

- Advise patients to immediately contact their healthcare provider for a fever, bruising, or bleeding. Advise patients of the need for monitoring of blood counts *[see Warnings and Precautions (5.3)]*.

Hypersensitivity

- Inform patients of the signs and symptoms of hypersensitivity. Advise patients to immediately report symptoms of hypersensitivity *[see Warnings and Precautions (5.4)]*.

Latex Allergy

- The double balloon catheter component of the HEPZATO KIT Hepatic Delivery System contains natural rubber latex which may cause allergic reactions in latex-sensitive individuals *[see Contraindications (4)]*.

Gastrointestinal

- Advise patients to report symptoms of nausea, vomiting and diarrhea, so that appropriate antiemetic and/or antidiarrheal medications can be administered *[see Warnings and Precautions (5.5)]*.

Secondary Malignancies

- Advise patients that treatment with HEPZATO has the potential long-term risk of secondary malignancy *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with HEPZATO and for 6 months after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking HEPZATO *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with HEPZATO and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with HEPZATO and for one week after the last dose *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.2)]*

Infertility

- Inform both females and males of reproductive potential about the risk of infertility *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.3)]*.

HEPZATO (melphalan) for Injection

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