

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MARQIBO safely and effectively. See **Full Prescribing Information** for MARQIBO.

Marqibo® (vinCRISTine sulfate LIPOSOME injection), for intravenous use
Initial U.S. Approval: 2012

WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES

See full prescribing information for complete boxed warning.

- Marqibo is for intravenous use only and is fatal if given by other routes. Death has occurred with intrathecal use. (5.1)
- Marqibo (vinCRISTine sulfate LIPOSOME injection) has different dosage recommendations than vinCRISTine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdose. (2.1, 5.1)

INDICATIONS AND USAGE

Marqibo is a vinca alkaloid indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.1).

DOSAGE AND ADMINISTRATION

- Intravenous use only. Do not administer by any other route (2.1)
- Administer Marqibo at a dose of 2.25 mg/m² intravenously over 1 hour once every 7 days (2.2).

DOSAGE FORMS AND STRENGTHS

Kit for Injection: After preparation, each single-dose vial of Marqibo (vinCRISTine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate (3).

CONTRAINDICATIONS

- Demyelinating conditions including Charcot-Marie-Tooth syndrome (4)
- Hypersensitivity to vincristine sulfate or any of the other components of Marqibo (vinCRISTine sulfate LIPOSOME injection) (4)
- For intrathecal administration (4)

WARNINGS AND PRECAUTIONS

- **Extravasation Tissue Injury:** Extravasation causes tissue injury. If suspected, discontinue infusion immediately and consider local treatment measures (5.2)
- **Neurologic Toxicity:** Monitor patients for peripheral motor and sensory, central and autonomic neuropathy. Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment. Interrupt, dose reduce, or discontinue Marqibo based on severity (2.3, 5.3)
- **Myelosuppression:** Neutropenia, thrombocytopenia, or anemia may occur. Monitor blood counts prior to each dose of Marqibo. Consider Marqibo dose delay or reduction, as well as supportive care measures for grade 3 or 4 reactions (5.4)
- **Tumor Lysis Syndrome:** Anticipate, monitor for, and manage (5.5)
- **Constipation and Bowel Obstruction:** Institute a prophylactic bowel regimen to prevent potential constipation, bowel obstruction, and/or paralytic ileus. Use additional laxative products as needed (5.6)
- **Fatigue:** Severe fatigue can occur. Consider dose delay, reduction or discontinuation as appropriate (5.7)
- **Hepatic Toxicity:** Fatal liver toxicity and increased AST occurred. Monitor hepatic function tests. Interrupt or dose reduce as appropriate (5.8)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception (5.9, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 30%) are constipation, nausea, pyrexia, fatigue, peripheral neuropathy, febrile neutropenia, diarrhea, anemia, decreased appetite, and insomnia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Acrotech Biopharma LLC at 1-888 292 9617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use (7.1)
- **P-gp Inhibitors or Inducers:** Avoid concomitant use (7.1)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed (8.2)
- **Infertility:** Can impair fertility (8.3)
- **Pediatric Use:** The safety and effectiveness of Marqibo in pediatric patients has not been established (8.4)

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FULL PRESCRIBING INFORMATION

WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES

- Marqibo is for intravenous use only and is fatal if given by other routes. Death has occurred with intrathecal administration [see *Warnings and Precautions (5.1)*].
- Marqibo (vinCRISTine sulfate LIPOSOME injection) has different dosage recommendations than vinCRISTine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

Marqibo® is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

This indication is approved under accelerated approval based on overall response rate [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

For Intravenous Use only. Fatal if given by other routes [see *Warnings and Precautions (5.1)*].

Marqibo (vinCRISTine sulfate LIPOSOME injection) has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage [see *Warnings and Precautions (5.1)*].

2.2 Recommended Dosage

The recommended dosage of Marqibo is 2.25 mg/m² intravenously over 1 hour once every 7 days.

2.3 Dosage Modifications: Peripheral Neuropathy

Marqibo is contraindicated in patients with demyelinating conditions, including Charcot-Marie-Tooth syndrome [see *Contraindications (4)*]. Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment [see *Warnings and Precautions (5.3)*]. For dose or schedule modifications guidelines for patients who experience peripheral neuropathy, see [Table 1](#).

Table 1. Recommended Dosage Modifications for Marqibo-related Peripheral Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms^a	Modification of Dose and Regimen
If the patient develops Grade 3 (severe symptoms; limiting self-care activities of daily living [ADL] ^b) or persistent Grade 2 (moderate symptoms; limiting instrumental ADL ^c) peripheral neuropathy:	Interrupt Marqibo. If the peripheral neuropathy remains at Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1 or 2, reduce the Marqibo dose to 2 mg/m ² .
If the patient has persistent Grade 2 peripheral neuropathy after the first dose reduction to 2 mg/m ² :	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If peripheral neuropathy recovers to Grade 1, reduce the Marqibo dose to 1.825 mg/m ² .
If the patient has persistent Grade 2 peripheral neuropathy after the second dose reduction to 1.825 mg/m ² :	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the toxicity recovers to Grade 1, reduce the Marqibo dose to 1.5 mg/m ² .

^a Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

^b Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

^c Instrumental ADL: refers to preparing meals, shopping for groceries and clothes, using telephone, and managing money.

2.4 Preparation

Items Required by the Pharmacy to Prepare Marqibo

- Marqibo Kit
- Water bath^a or block heater^b
- Calibrated thermometer^a (0°C to 100°C)
- Calibrated electronic timer^a
- Sterile venting needle or other suitable device equipped with a sterile 0.2 micron filter
- 1 mL or 3 mL sterile syringe with needle, and
- 5 mL sterile syringe with needle.
- Tongs^c

^a The manufacturer will provide the water bath, calibrated thermometer, and calibrated electronic timer to the medical facility at the initial order of Marqibo and will replace them every 2 years.

^b The manufacturer will provide the block heater to the medical facility at the initial order of Marqibo. The block heater will be replaced every 5 years.

^c The manufacturer will provide tongs to the medical facility at the initial order of Marqibo.

Preparation Instructions for Marqibo

Marqibo is a hazardous drug. Follow applicable special handling and disposal procedures.¹

Call 1-888-292-9617 if you have questions about the preparation of Marqibo.

Marqibo takes approximately 60 to 90 minutes to prepare. The preparer should have dedicated uninterrupted time to prepare Marqibo due to the extensive monitoring of temperature and time required for the preparation.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Marqibo. The preparation steps of Marqibo that involve mixing the Sodium Phosphate Injection, Spingomyelin/

Cholesterol Liposome Injection, and VinCRISTine Sulfate Injection must be done in a biological safety cabinet or by established pharmacy safety procedures for the preparation of sterile injectable formulations and hazardous drugs. However, the preparation steps that involve placement of the vial in the water bath must be done outside of the sterile area.

Do not use with in-line filters. Do not mix with other drugs.

Water Bath Process

1. Fill a water bath with water to a level of at least 8 cm (3.2 inches) measured from the bottom and maintain this minimum water level throughout the procedure. The water bath must remain outside of the sterile area.
2. Place a calibrated thermometer in the water bath to monitor water temperature and leave it in the water bath until the procedure has been completed.
3. Preheat water bath to 63°C to 67°C. Maintain this water temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the Marqibo Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2 micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRISTine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.
9. Withdraw 5 mL of VinCRISTine Sulfate Injection.
10. Inject 5 mL of VinCRISTine Sulfate Injection into the Sodium Phosphate Injection vial.
11. Remove the venting needle and gently invert the Sodium Phosphate Injection vial 5 times to mix. **DO NOT SHAKE.**
12. Fit Flotation Ring around the neck of the Sodium Phosphate Injection vial.
13. Confirm that the water bath temperature is at 63°C to 67°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRISTine Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and **place into the water bath for 10 minutes** using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 63°C to 67°C.
14. **IMMEDIATELY** after placing the Sodium Phosphate Injection vial into the water bath, record the constitution start time and water temperature on the Marqibo Overlabel.
15. **At the end of the 10 minutes using the water bath**, confirm that the water temperature is 63°C to 67°C using the calibrated thermometer. Remove the vial from the water bath (use tongs to prevent burns) and remove the Flotation Ring.
16. Record the final constitution time and the water temperature on the Marqibo Overlabel.
17. Dry the exterior of the Sodium Phosphate Injection vial with a clean paper towel, affix Marqibo (vinCRISTine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. **DO NOT SHAKE.**
18. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
19. Marqibo (vinCRISTine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. **ONCE PREPARED, STORE AT CONTROLLED ROOM TEMPERATURE (15°C to 30°C, 59°F to 86°F) FOR NO MORE THAN 12 HOURS.**

20. Swab the top of the vial now containing Marqibo with a sterile alcohol pad and return the vial back into the biological safety cabinet.
21. Calculate the patient's Marqibo dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo dose from an infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
22. Inject the dose of Marqibo into the infusion bag to result in a final volume of 100 mL.
23. Complete the information required on the Infusion Bag Label and apply to the infusion bag.
24. Finish administration of the diluted product within 12 hours of the initiation of Marqibo preparation.
25. Empty, clean, and dry the water bath after each use.
26. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Block Heater Process

Note: Do NOT use water with the block heater preparation process.

Note: The flotation ring included with the Marqibo kit is not required for the block heater application.

1. Arrange the three heater blocks in the block heater such that the block holding the constitution vial is centered between the two other blank heater blocks. See the illustration below.



2. Place a calibrated thermometer in the block opening adjacent to the vial well to monitor the temperature. Leave the thermometer in the block opening until the procedure has been completed.
3. Turn on the block heater and set the controller to 75°C. Verify the block temperature by checking that the thermometer inserted in the block reads 75 ± 2°C. Equilibrate the heating block at 75 ± 2°C for 15 minutes. Maintain this block temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the Marqibo Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2 micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRISStine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.

9. Withdraw 5 mL of VinCRISTine Sulfate Injection.
10. Inject 5 mL of VinCRISTine Sulfate Injection into the Sodium Phosphate Injection vial.
11. Remove the venting needle and gently invert the Sodium Phosphate Injection vial 5 times to mix. **DO NOT SHAKE.**
12. Confirm that the block heater temperature is at 73°C to 77°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRISTine Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and **place into the block heater for 18 minutes** using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 73°C to 77°C.
13. **IMMEDIATELY** after placing the Sodium Phosphate Injection vial into the block heater, record the constitution start time and block heater temperature on the Marqibo Overlabel. Use only the calibrated thermometer inserted in the block to monitor temperature.
14. **At the end of the 18 minutes using the block heater**, confirm that the block heater temperature is 73°C to 77°C using the calibrated thermometer. Remove the vial from the block heater (use tongs to prevent burns).
15. Record the final constitution time and the block heater temperature on the Marqibo Overlabel.
16. Affix Marqibo (vinCRISTine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. **DO NOT SHAKE.**
17. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
18. Marqibo (vinCRISTine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. **ONCE PREPARED, STORE AT CONTROLLED ROOM TEMPERATURE (15°C to 30°C, 59°F to 86°F) FOR NO MORE THAN 12 HOURS.**
19. Swab the top of the vial now containing Marqibo with a sterile alcohol pad and return the vial back into the biological safety cabinet.
20. Calculate the patient's Marqibo dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo dose from an infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
21. Inject the dose of Marqibo into the infusion bag to result in a final volume of 100 mL.
22. Complete the information required on the Infusion Bag Label and apply to the infusion bag.
23. Finish administration of the diluted product within 12 hours of the initiation of Marqibo preparation.
24. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

3 DOSAGE FORMS AND STRENGTHS

Kit for Injection: Following the preparation procedure according to section 2.4, each single-dose vial of Marqibo (vinCRISTine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate.

4 CONTRAINDICATIONS

Marqibo is contraindicated in patients with demyelinating conditions, including Charcot-Marie-Tooth syndrome.

Marqibo is contraindicated in patients with hypersensitivity to vincristine sulfate or any of the other components of Marqibo (vinCRISTine sulfate LIPOSOME injection).

Marqibo is contraindicated for intrathecal administration.

5 WARNINGS AND PRECAUTIONS

5.1 For Intravenous Use Only: Fatal if Given by Other Routes

Fatal if given by other routes. Death has occurred with intrathecal use.

Marqibo (vinCRISTine sulfate LIPOSOME injection) has different dosage recommendations than vinCRISTine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage [*see Dosage and Administration (2.1)*].

5.2 Extravasation Tissue Injury

Extravasation can occur with Marqibo and extravasation causes tissue injury. Only administer through a secure and free-flowing venous access line. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures.

5.3 Neurologic Toxicity

Sensory and motor neuropathies are common and are cumulative. Monitor patients for symptoms of peripheral motor and sensory, central and autonomic neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment. Orthostatic hypotension may occur. The risk of neurologic toxicity is greater if Marqibo is administered to patients with preexisting neuromuscular disorders or when other drugs with risk of neurologic toxicity are being given. In the studies of relapsed and/or refractory adult ALL patients, Grade ≥ 3 neuropathy events occurred in 32.5% of patients.

Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment. Interrupt, reduce the dose, or discontinue Marqibo based on severity [*see Dosage and Administration (2.3)*].

5.4 Myelosuppression

Neutropenia, thrombocytopenia, or anemia may occur with Marqibo. Monitor complete blood counts prior to each dose of Marqibo. For Grade 3 or 4 neutropenia, thrombocytopenia, or anemia, consider Marqibo dose delay or reduction, as well as supportive care measures.

5.5 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients with ALL receiving Marqibo. Anticipate, monitor for, and manage as appropriate.

5.6 Constipation and Bowel Obstruction

Ileus, bowel obstruction, and colonic pseudo-obstruction have occurred. Marqibo can cause constipation [*see Adverse Reactions (6)*].

Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction, and paralytic ileus. Consider adequate dietary fiber intake, hydration, and stool softeners. Use additional laxative products as needed.

5.7 Fatigue

Marqibo can cause severe fatigue. Consider dose delay, reduction, or discontinuation of Marqibo as appropriate.

5.8 Hepatic Toxicity

Fatal hepatic toxicity and increased aspartate aminotransferase (AST) occurred. Grade ≥ 3 increased AST occurred in 6% to 11% of patients in clinical trials. Monitor hepatic function tests. Interrupt or reduce the dose of Marqibo as appropriate.

5.9 Embryo-Fetal Toxicity

Based on findings from nonclinical studies and the mechanism of action, Marqibo can cause fetal harm when administered to a pregnant woman. In toxicology studies in rats, vincristine sulfate liposome injection was teratogenic and caused embryo-fetal mortality at exposures less than those reported in patients at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Marqibo and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Marqibo and for 3 months after the last dose [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

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

- For Intravenous Use Only [*see Warnings and Precautions (5.1)*]
- Extravasation Tissue Injury [*see Warnings and Precautions (5.2)*]
- Neurologic Toxicity [*see Warnings and Precautions (5.3)*]
- Myelosuppression [*see Warnings and Precautions (5.4)*]
- Tumor Lysis Syndrome [*see Warnings and Precautions (5.5)*]
- Constipation and Bowel Obstruction [*see Warnings and Precautions (5.6)*]
- Fatigue [*see Warnings and Precautions (5.7)*]
- Hepatic Toxicity [*see Warnings and Precautions (5.8)*]

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 cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Acute Lymphoblastic Leukemia

Relapsed or Refractory Philadelphia Chromosome Negative ALL

The safety of Marqibo was evaluated in a total of 83 adults in two trials: study 1 and study 2. Patients received Marqibo 2.25 mg/m² once every seven days. Adverse reactions were observed in 100% of patients. The most common adverse reactions (>30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%).

Adverse reactions of Grade 3 or greater were reported in 96% of patients. Adverse reactions of Grade 3 or greater and occurring in ≥5% of patients are summarized in [Table 2](#).

Table 2. Most Commonly Reported (> 5%) Grade 3^a or Greater Adverse Reactions among 83 Patients Receiving the Clinical Dosing Regimen

Adverse Reactions Grade ≥ 3	Study 1 and 2 (N=83) n (%)
<i>Blood and Lymphatic System Disorders</i>	47 (56.6)
Febrile Neutropenia	26 (31.3)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
<i>Infections</i>	33 (39.8)
Pneumonia	7 (8.4)
Septic Shock	5 (6.0)
Staphylococcal Bacteremia	5 (6.0)
<i>Neuropathy^b</i>	27 (32.5)
Peripheral Sensory and Motor Neuropathy	14 (16.7)
Constipation	4 (4.8)
Ileus, Colonic Pseudo-Obstruction	5 (6.0)
Asthenia	4 (4.8)
Muscular Weakness	1 (1.2)
<i>Respiratory Thoracic and Mediastinal Disorders</i>	17 (20.5)
Respiratory Distress	5 (6.0)
Respiratory Failure	4 (4.8)
<i>General Disorders and Administration Site Condition</i>	31 (37.3)
Pyrexia	12 (14.5)
Fatigue	10 (12.0)
Pain	7 (8.4)
<i>Gastrointestinal Disorders</i>	21 (25.3)
Abdominal Pain	7 (8.4)
<i>Investigations</i>	20 (24.1)
Aspartate Aminotransferase Increased	6 (7.2)
<i>Vascular Disorders</i>	8 (9.6)
Hypotension	5 (6.0)
<i>Psychiatric Disorders</i>	9 (10.8)
Mental Status Changes	3 (3.6)
<i>Cardiac Disorders</i>	9 (10.8)
Cardiac Arrest	5 (6.0)
<i>Renal and Urinary Disorders</i>	6 (7.2)
<i>Musculoskeletal and Connective Tissue Disorders</i>	7 (8.4)

^a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

^b Including neuropathy-associated adverse reactions.

A total of 76% of patients experienced serious adverse reactions during the studies. The most frequent serious adverse reactions included febrile neutropenia (20%), pyrexia (13%), hypotension (7%), respiratory distress (6%), and cardiac arrest (6%).

Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The most frequent adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%).

Dose reduction, delay, or omission occurred in 53% of patients.

Adverse reactions related to neuropathy and leading to treatment discontinuation were decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain, each reported in at least 1 patient.

Deaths occurred in 23% of patients in study 1. The non-leukemia related causes of deaths were brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multi system organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1).

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Marqibo

Strong CYP3A Inhibitors

Concomitant use of strong CYP3A4 inhibitors may increase the concentrations of vincristine, which may increase the risk of adverse reactions. Avoid concomitant use of strong CYP3A inhibitors.

Strong CYP3A Inducers

Concomitant use of strong CYP3A4 inducers may decrease the concentrations of vincristine, which may decrease antitumor activity. Avoid concomitant use of strong CYP3A inducers.

P-glycoprotein Inhibitors and Inducers

Concomitant use of Marqibo with P-glycoprotein inhibitors or inducers may alter the pharmacokinetics or pharmacodynamics of vincristine. Avoid the concomitant use of P-gp inhibitors or inducers.

7.2 Effects of Marqibo on Other Drugs

Phenytoin

Simultaneous oral or intravenous administration of phenytoin and chemotherapy combinations that included non-liposomal vincristine sulfate have been reported to reduce blood levels of phenytoin and to increase seizure activity. Monitor phenytoin blood levels and seizure activity as appropriate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from nonclinical studies and its mechanism of action, Marqibo can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*, *Nonclinical Toxicology (13.1)*]. There are insufficient data on use of vincristine sulfate in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, intravenous administration of vincristine sulfate liposome injection to pregnant rats during organogenesis caused adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats were administered vincristine sulfate liposome injection intravenously during the period of organogenesis at vincristine sulfate doses of 0.022 to 0.09 mg/kg/day. Drug-related adverse effects included fetal malformations (skeletal and visceral), decreases in fetal weights, increased numbers of early resorptions and post-implantation losses, and decreased maternal body weights. Malformations were observed at doses ≥ 0.044 mg/kg/day in animals at systemic exposures approximately 20-40% of those reported in patients at the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of vincristine sulfate or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Marqibo and for at least 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Marqibo can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating Marqibo.

Contraception

Females

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

Males

Based on genotoxicity findings with non-liposomal vincristine, advise males with female partners of reproductive potential to use effective contraception during treatment with Marqibo and for 3 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Based on findings in humans with non-liposomal vincristine sulfate and in animals administered vincristine sulfate liposome injection, Marqibo may impair fertility.

Gonadal dysfunction has been reported in both male and female post-pubertal patients who received multi-agent chemotherapy, including non-liposomal vincristine sulfate. The degree to which testicular or ovarian functions are affected is age-, dose-, and agent-dependent. Recovery may occur in some, but not all patients.

In animals, adverse effects on male reproductive organs were not reversible after a recovery period [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients in clinical studies of Marqibo, 11% were aged 65 years or older. Clinical studies of Marqibo did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Monitor patients closely for adverse reactions, including hepatic toxicity. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The influence of severe hepatic impairment on the exposure, safety and efficacy of Marqibo has not been evaluated.

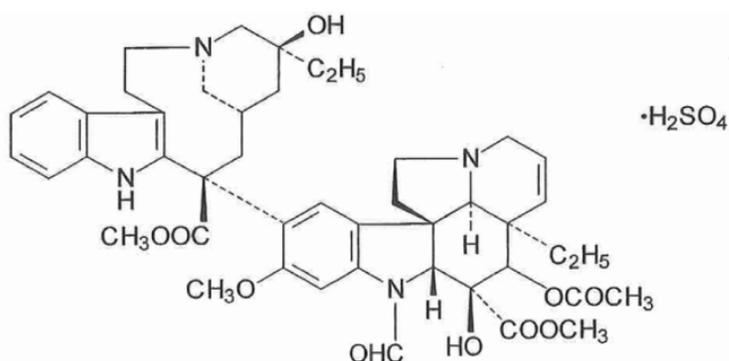
10. OVERDOSAGE

When Marqibo (vinCRISStine sulfate LIPOSOME injection) was administered at a dose of 2.4 mg/m² (1.1 times the recommended dose), severe adverse reactions, including Grade 3 motor neuropathy, Grade 4 grand mal seizure, and Grade 4 increased AST and bilirubin were reported in 1 patient each.

11 DESCRIPTION

Marqibo (vinCRISStine sulfate LIPOSOME injection) is vincristine encapsulated in sphingomyelin/cholesterol liposomes for intravenous use.

The active ingredient in Marqibo is vincristine sulfate. Vincristine sulfate is a vinca alkaloid isolated as a 1:1 sulfate salt from the periwinkle plant (*Catharanthus roseus*). It is a hygroscopic, white to slightly yellowish crystalline powder that is soluble in water. It has a molecular weight of 923.04 (salt form) / 824.98 (base form) and a molecular formula of C₄₆H₅₆N₄O₁₀ • H₂SO₄. The chemical name for vincristine sulfate is 22-oxovincalcoloblastine and it has the following chemical structure:



Vincristine is encapsulated in a Sphingomyelin/Cholesterol Liposome. The lipid components in the liposome are sphingomyelin and cholesterol at a molar ratio of approximately 60:40 (mol:mol).

After preparation, each vial of Marqibo contains 5 mg vincristine sulfate, 500 mg mannitol, 73.5 mg sphingomyelin, 29.5 mg cholesterol, 35.4 mg sodium citrate, 33.6 mg citric acid, 355 mg sodium phosphate, 225 mg sodium chloride, and not more than 0.1% ethanol.

Marqibo (vinCRISStine sulfate LIPOSOME injection) appears as a white to off-white, translucent suspension, essentially free of visible foreign matter and aggregates, comprised of sphingomyelin/cholesterol liposomes, with an approximate liposome mean diameter of 100 nm. Greater than 95% of the drug is encapsulated in the liposomes.

The Marqibo Kit component vials for the preparation of Marqibo (vinCRISStine sulfate LIPOSOME injection) include:

- VinCRISStine Sulfate Injection, USP (5 mg/5 mL). Each VinCRISStine Sulfate Injection vial consists of 5 mg/5 mL vincristine sulfate (which is equivalent to 4.5 mg/5 mL vincristine free base) and 500 mg/5 mL mannitol. Sodium hydroxide and sulfuric acids as pH adjuster.
- Sphingomyelin/Cholesterol Liposome Injection (103 mg/mL). Each Sphingomyelin/Cholesterol Liposome Injection vial consists of 73.5 mg/mL sphingomyelin, 29.5 mg/mL cholesterol, 33.6 mg/mL citric acid, 35.4 mg/mL sodium citrate, and not more than 0.1% ethanol.
- Sodium Phosphate Injection (355 mg/25 mL). Each Sodium Phosphate Injection vial consists of 355 mg/25 mL dibasic sodium phosphate and 225 mg/25 mL sodium chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Marqibo is a sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine sulfate. Non-liposomal vincristine sulfate binds to tubulin, altering the tubulin polymerization equilibrium, resulting in altered microtubule structure and function. Non-liposomal vincristine sulfate stabilizes the spindle apparatus, preventing chromosome segregation, triggering metaphase arrest and inhibition of mitosis.

12.3 Pharmacokinetics

The pharmacokinetics of total plasma vincristine sulfate in patients who received Marqibo 2.25 mg/m² administered as a 1-hour intravenous infusion are summarized in Table 3. The vincristine sulfate levels reported in Table 3 reflect liposome-encapsulated drug that may not be immediately bioavailable and are not directly comparable to plasma levels of vincristine sulfate after administration of non-liposomal vincristine sulfate, which is immediately bioavailable.

Table 3. Pharmacokinetic Parameters from Patients with Acute Lymphoblastic Leukemia who Received Marqibo 2.25 mg/m^{2a}

Variable	N	Mean	SE	Median	Range
AUC _{0-INF} (h•ng/mL)	13	14566	1766	13680	7036-26074
CL (mL/h)	12	345	100	302	148-783
C _{max} (ng/mL)	13	1220	64	1230	919-1720

^a Dose was administered as a 1-hour infusion.

Elimination

Metabolism

Vincristine is metabolized by CYP3A4.

Excretion

Following intravenous administration of Marqibo, less than 8% of the administered dose was eliminated in urine over 96 hours, which is similar to the urinary excretion of non-liposomal vincristine sulfate. Following non-liposomal vincristine sulfate infusion, fecal route accounted for 69% of the administered dose over 72 hours.

Specific Populations

Patients with Hepatic Impairment

Following the administration of Marqibo 1 mg/m² (0.44 times the recommended dose) every 14 days in patients with cancer and moderate hepatic impairment (Child-Pugh scores 7-8), the median (min-max) dose adjusted C_{max} was 399 ng/mL (217 – 531) and AUC_{0-inf} was 4926 ng*hr/mL (4650 – 9640). The change in pharmacokinetics in patients with moderate hepatic impairment are not considered clinically meaningful. The impact of severe hepatic impairment on the pharmacokinetics of vincristine is unknown.

Drug Interaction Studies

In Vitro Studies

Transporters: Vincristine is a substrate of P-glycoprotein in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with Marqibo or non-liposomal vincristine sulfate. Based on the mechanism of action and genotoxicity findings in nonclinical studies conducted with non-liposomal vincristine sulfate, Marqibo may be carcinogenic.

No genotoxicity studies have been conducted with Marqibo. Non-liposomal vincristine was genotoxic in in vitro and in vivo studies.

The single- and repeat-dose animal toxicology study results indicate that Marqibo can impair male fertility, consistent with the literature on non-liposomal vincristine sulfate. Administration of vincristine liposome injection to rats at dose levels comparable to the recommended clinical dose caused testicular degeneration and atrophy, and epididymal aspermia. Adverse effects in male reproductive organs were not reversible following a 14 day recovery period.

13.2 Animal Toxicology and/or Pharmacology

In a repeat-dose comparative toxicology study in rats, vincristine sulfate liposome injection or non-liposomal vincristine sulfate was administered to animals intravenously once per week for 6 weeks. Clinical signs of toxicity consistent with neurotoxicity were greater with vincristine sulfate liposome injection than with non-liposomal vincristine sulfate at equal vincristine sulfate doses of 2 mg/m²/week and included uncoordinated movements, weakness, reduced muscle tone, and limited usage of the limbs. Vincristine sulfate liposome injection induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of non-liposomal vincristine sulfate.

14 CLINICAL STUDIES

14.1 Acute Lymphoblastic Leukemia

Marqibo was studied in an international, open-label, multi-center, single-arm trial (Study 1). Eligible patients were 18 years of age or older with Philadelphia chromosome negative ALL in second or greater relapse or whose disease progressed after two or greater treatment lines of anti-leukemia therapy. Patients had to have achieved a complete remission (CR) to at least one prior anti-leukemia chemotherapy, defined by a leukemia-free interval of equal or more than 90 days. Patients were not eligible for immediate hematopoietic stem cell transplantation (HSCT) at the time of screening and enrollment.

Patients received intravenous Marqibo monotherapy at 2.25 mg/m² over 60 minutes every 7 days. Concomitant corticosteroids were not permitted beyond Day 5.

The treated population included 65 patients who received at least 1 dose of Marqibo. All of the treated patients had received prior vincristine sulfate and 80% had evidence of residual neuropathy at study baseline. Among treated patients, 51% were male, 86% were white, 45% were under 30 years of age, 11% were age 65 or older, 48% had undergone prior HSCT, 51% had received 3 or more prior therapies, and 45% were refractory to their immediate prior therapy. Disease characteristics were 85% precursor B-cell ALL and 15% precursor T-cell ALL. In addition, 22 of 65 (34%) treated patients did not receive asparaginase products prior to enrollment. Efficacy results are shown in [Table 4](#).

Table 4. Study 1 Results

	Study 1 (N=65) n (%)
Complete remission (CR)	3 (4.6)
CR with incomplete blood count recovery (CRi)	7 (10.8)
CR + CRi (95% CI ^a)	10 (15.4) (7.6 – 26.5)
MEDIAN DURATION of CR or CRi:	Days (95% CI)
Based on the first date of CR or CRi to the date of the last available histologic assessment of the same response (n=8)	28 (7, 36)
Based on the first date of CR or CRi to date of documented relapse, death, or subsequent chemotherapies including hematopoietic stem cell transplant (HSCT) (n=10)	56 (9, 65)

a CI = Confidence interval (Clopper-Pearson).

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

The Marqibo Kit (NDC # 72893-008-03) contains:

- Vial containing VinCRISTine Sulfate Injection, USP 5 mg/5 mL (1 mg/mL) – NDC # 72893-012-05
- Vial containing Sphingomyelin/Cholesterol Liposome Injection 103 mg/mL – NDC # 72893-011-05
- Vial containing Sodium Phosphate Injection 355 mg/25 mL (14.2 mg/mL) – NDC # 72893-010-05
- Flotation Ring
- Overlabel for Sodium Phosphate Injection vial containing constituted Marqibo (vinCRISTine sulfate LIPOSOME injection), 5 mg/31 mL (0.16 mg/mL)
- Infusion Bag Label

The prepared liposome product should be administered within 12 hours of the initiation of Marqibo preparation.

Store the Marqibo Kit in the refrigerator at 2°C to 8°C. Do Not Freeze

Marqibo is a hazardous drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Healthcare providers are advised to discuss the following with patients prior to treatment with Marqibo:

Extravasation Tissue Injury

Advise patients to report immediately any burning or local irritation during or after the infusion [*see Warnings and Precautions (5.2)*].

Neurologic Toxicity and Fatigue

Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the feet or hands [*see Warnings and Precautions (5.3)*].

Marqibo may cause fatigue and symptoms of peripheral neuropathy. Advise patients not to drive or operate machinery if they experience any of these symptoms [*see Warnings and Precautions (5.3, 5.7)*].

Constipation and Bowel Obstruction

Patients receiving Marqibo may experience constipation. Advise patients how to avoid constipation by a diet high in bulk fiber, fruits and vegetables and adequate fluid intake, as well as use of a stool softener. Instruct patients to seek medical advice if they experience symptoms of constipation such as bowel movement infrequency, abdominal pain, bloating, diarrhea, nausea, or vomiting [*see Warnings and Precautions (5.6)*].

Myelosuppression

Instruct patients to notify their healthcare providers if they experience fever, productive cough, or decreased appetite [*see Warnings and Precautions (5.4)*].

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.9), Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with Marqibo and for 6 months after the last dose [*see Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment with Marqibo and for 3 months after the last dose. [*see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)*].

Lactation

Advise women not to breastfeed during treatment with Marqibo and for 1 week after the last dose [*see Use in Specific Populations (8.2)*].

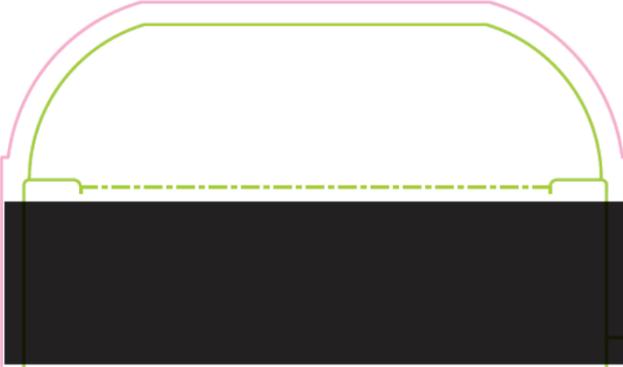
Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [*see Drug Interactions (7)*].

Manufactured for:

Acrotech Biopharma LLC
East Windsor, NJ 08520

29.5 mg cholesterol (b) (4) sodium citrate, (b) citric acid,



Marqibo
(vinCRIS^tine sulfate LIPOSOME injection)
NDC 72893-008-03
Rx only

For Intravenous Use Only
Fatal If Given By Other Routes
Single Use Vials – Discard Unused Portion

NDC 72893-008-03 Rx only
Marqibo
(vinCRIS^tine sulfate LIPOSOME injection)
Marqibo Kit Contents:
• Sodium Phosphate Injection Vial 355 mg/25 mL (14.2 mg/mL)
• Sphingomyelin-Cholesterol Liposome Injection Vial 103 mg/mL
• VinCRIS^tine Sulfate Injection, USP Vial 5 mg/5 mL (1 mg/mL)
• Floatation Ring
• Overlabel and Infusion Bag Label
• Package Insert
Store kit at 2°C to 8°C (36°F to 46°F). **DO NOT FREEZE.**

For Intravenous Use Only
Fatal If Given By Other Routes
Single Use Vials – Discard Unused Portion 603698



603698

Marqibo
(vinCRIS^tine sulfate LIPOSOME injection)

Sodium Phosphate Injection Ingredients:
dibasic sodium phosphate, heptahydrate, USP, sodium chloride, USP, water for injection, USP
Sphingomyelin-Cholesterol Liposome Injection Ingredients:
sphingomyelin, cholesterol HP, citric acid, monohydrate, USP, dehydrated alcohol (ethanol), USP, sodium citrate, dihydrate, USP, water for injection, USP
VinCRIS^tine Sulfate Injection, USP Ingredients:
Vincristine sulfate, USP, mannitol, USP, water for injection, USP, Sodium hydroxide, USP and sulfuric acid, USP as pH adjuster.
Marqibo Kit Ingredients:
5 mg vincristine sulfate, 500 mg mannitol, 73.5 mg sphingomyelin, 29.5 mg cholesterol, 35.4 mg sodium citrate, 33.6 citric acid, 355 mg sodium phosphate, 225 mg sodium chloride, and not more than 0.1% ethanol.

For Intravenous Use Only
Fatal If Given By Other Routes

Manufactured for: Acrotech Biopharma LLC
East Windsor, NJ 08520

NDC 72893-008-03 Rx only
Marqibo
(vinCRIS^tine sulfate LIPOSOME injection)

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• Floatation Ring
• Overlabel and Infusion Bag Label
• Package Insert
Store kit at 2°C to 8°C (36°F to 46°F). **DO NOT FREEZE.**

For Intravenous Use Only
Fatal If Given By Other Routes
Single Use Vials – Discard Unused Portion

Marqibo
(vinCRIS^tine sulfate LIPOSOME injection)

DIRECTIONS
• Store kit at 2°C to 8°C (36°F to 46°F). **DO NOT FREEZE.** Retain vials in kit until time of use to protect from light.
• Preparation: Marqibo is prepared from the components in the Marqibo Kit according to the instructions in the package insert. Following preparation, Marqibo must be diluted before use.
• Dosage: See package insert for dosage and administration information.

For Intravenous Use Only
Fatal If Given By Other Routes



(b) (4)



Ramesh
Raghavachari

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