CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202497Orig1s000

<u>LABELING</u>

1.14 Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Marqibo® (vinCRIStine sulfate LIPOSOME injection) safely and effectively. See Full Prescribing Information for Marqibo (vinCRIStine sulfate LIPOSOME injection).

Marqibo® (vinCRIStine sulfate LIPOSOME injection) for intravenous infusion

Initial U.S. Approval: 2012

WARNING

See full prescribing information for complete boxed warning.

- **For Intravenous Use Only – Fatal if Given by Other Routes (5.1)**
- **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.**

----------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 based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified (1.1).

----------DOSAGE AND ADMINISTRATION----------

Intravenous use only. Do not administer by any other route (2)

Administer Marqibo at a dose of 2.25 mg/m^2 intravenously over 1 hour once every 7 days (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

The final drug product is prepared on site from the components in the Marqibo Kit. After preparation, each single-dose vial of Marqibo (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate (2.3.2).

----------CONTRAINDICATIONS----------

- Marqibo is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome (4)
- Marqibo is contraindicated in patients with hypersensitivity to vincristine sulfate or any of the other components of Marqibo (vinCRIStine sulfate LIPOSOME injection) (4)
- Marqibo is contraindicated for intrathecal administration (4)

----------WARNINGS AND PRECAUTIONS----------

- Intrathecal administration is fatal (5.1)
- Extravasation causes tissue injury (5.2)
- Neurologic toxicity: Monitor patients for peripheral motor and sensory, central and autonomic neuropathy, and reduce, interrupt, or discontinue dosing. Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment (2.2, 5.3)
- Myelosuppression: Monitor blood counts prior to each dose of Marqibo. Neutropenia, thrombocytopenia, or anemia may occur; consider Marqibo dose reduction or interruption and supportive care measures (5.4)
- Tumor lysis syndrome: Anticipate, monitor for, and manage (5.5)
- Constipation, bowel obstruction, and/or paralytic ileus: Institute a prophylactic bowel regimen to prevent potential constipation, bowel obstruction, and/or paralytic ileus (5.6)
- Fatigue: Severe fatigue can occur (5.7)
- Hepatic toxicity: Monitor liver function and modify or interrupt dosing (5.8)
- Embryofetal toxicity: Can cause fetal harm. Advise women of potential risk to the fetus (5.9, 8.1)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (incidence ≥ 30%) in clinical studies include constipation, nausea, pyrexia, fatigue, peripheral neuropathy, febrile neutropenia, diarrhea, anemia, decreased appetite, and insomnia (6.1).

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

----------DRUG INTERACTIONS----------

Marqibo is expected to interact with drugs known to interact with non-liposomal vincristine sulfate (7).

----------USE IN SPECIFIC POPULATIONS----------

Pediatric Use: The safety and effectiveness of Marqibo in pediatric patients has not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [July/2012

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FULL PRESCRIBING INFORMATION

WARNING

- **For Intravenous Use Only – Fatal if Given by Other Routes [*see Warnings and Precautions (5.1)*].**
- **Death has occurred with intrathecal administration.**
- **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**.

1 INDICATIONS AND USAGE

1.1 Adult ALL in Second or Greater Relapse

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 based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only. Fatal if Given by Other Routes.

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.

2.1 Recommended Dosage

The recommended dose of Marqibo is 2.25 mg/m^2 intravenously over 1 hour once every 7 days.

Marqibo is liposome-encapsulated vincristine.

2.2 Dose 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 Dose 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, managing money, etc.

2.3 Preparation and Handling

2.3.1 Items Required by the Pharmacy to Prepare Marqibo

- Marqibo Kit
- Water bath[a]
- 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.

[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.

2.3.2 Preparation Instructions for Marqibo (vinCRIStine sulfate LIPOSOME injection), 5 mg/31 mL (0.16 mg/mL)

Procedures for handling and disposal of anticancer drugs should be followed [*see References (15)*].

1.14 Labeling

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, Sphingomyelin/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.

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, 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.

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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.

3 DOSAGE FORMS AND STRENGTHS

Marqibo is prepared from the components in the Marqibo Kit. Following the preparation procedure according to section 2.3.2, 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. Death has occurred with intrathecal use.

5.2 Extravasation 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 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. Worsening neuropathy requires dose delay, reduction, or discontinuation of Marqibo [*see Dosage and Administration (2.2)*].

5.4 Myelosuppression

Monitor complete blood counts prior to each dose of Marqibo. If Grade 3 or 4 neutropenia, thrombocytopenia, or anemia develops, consider Marqibo dose modification 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.

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/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners, such as docusate. Additional treatments, such as senna, bisacodyl, milk of magnesia, magnesium citrate, and lactulose may be considered.

5.7 Fatigue

Marqibo can cause severe fatigue. Marqibo dose delay, reduction, or discontinuation may be necessary.

5.8 Hepatic Toxicity

Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred. Elevated levels of aspartate aminotransferase of Grade ≥3 occurred in 6-11% of patients in clinical trials. Monitor hepatic function tests. Reduce or interrupt Marqibo for hepatic toxicity.

5.9 Embryofetal Toxicity

Marqibo can cause fetal harm when administered to a pregnant woman. Vincristine sulfate liposome injection was teratogenic or caused embryo-fetal death in animals. Women of childbearing potential should avoid becoming pregnant while being treated with Marqibo. There are no adequate and well-controlled studies of Marqibo in pregnant women and there were no reports of pregnancy in any of the clinical studies in the Marqibo clinical development program. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- For intravenous use only [*see Warnings and Precautions (5.1)*]
- Extravasation tissue injury [*see Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [*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)*]

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6.1 Clinical Trials Safety 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.

Integrated Summary of Safety in Relapsed and/or Refractory Ph- Adult Acute Lymphoblastic Leukemia

Marqibo, at a dose of 2.25 mg/m^2 weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. 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[a] 3 or Greater Adverse Reactions among 83 Patients Receiving the Clinical Dosing Regimen

Adverse Reactions Grade ≥ 3	Study 1 and 2 (N=83) n (%)
Blood and Lymphatic System Disorders	*47 (56.6)*
Febrile Neutropenia	26 (31.3)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
Infections	*33 (39.8)*
Pneumonia	7 (8.4)
Septic Shock	5 (6.0)
Staphylococcal Bacteremia	5 (6.0)
Neuropathy[b]	*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)
Respiratory Thoracic and Mediastinal Disorders	*17 (20.5)*
Respiratory Distress	5 (6.0)
Respiratory Failure	4 (4.8)
General Disorders and Administration Site Condition	*31 (37.3)*
Pyrexia	12 (14.5)
Fatigue	10 (12.0)
Pain	7 (8.4)
Gastrointestinal Disorders	*21 (25.3)*
Abdominal Pain	7 (8.4)
Investigations	*20 (24.1)*
Aspartate Aminotransferase Increased	6 (7.2)
Vascular Disorders	*8 (9.6)*
Hypotension	5 (6.0)
Psychiatric Disorders	*9 (10.8)*
Mental Status Changes	3 (3.6)
Cardiac Disorders	*9 (10.8)*
Cardiac Arrest	5 (6.0)
Renal and Urinary Disorders	*6 (7.2)*
Musculoskeletal and Connective Tissue Disorders	*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 75.9% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included febrile neutropenia (20.5%), pyrexia (13.3%), hypotension (7.2%), respiratory distress (6.0%), and cardiac arrest (6.0%).

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

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

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

No formal drug interaction studies have been conducted with Marqibo. Marqibo is expected to interact with drugs known to interact with non-liposomal vincristine sulfate.

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

7.1 CYP3A Interactions

Vincristine sulfate, the active agent in Marqibo, is a substrate for cytochrome P450 3A isozymes (CYP3A); therefore, the concomitant use of strong CYP3A inhibitors should be avoided (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin). Similarly, the concomitant use of strong CYP3A inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort).

7.2 P-glycoprotein Interactions

Vincristine sulfate, the active agent in Marqibo, is also a substrate for P-glycoprotein (P-gp). The effect of concomitant use of potent P-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo. Therefore the concomitant use of potent P-gp inhibitors or inducers should be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.9)*]

Based on its mechanism of action and findings from animal studies, Marqibo can cause fetal harm when administered to pregnant women.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. In an embryofetal 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.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Safety and effectiveness in elderly individuals have not been established. 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 Renal Impairment

The influence of renal impairment on the safety, efficacy, and pharmacokinetics of Marqibo has not been evaluated.

8.7 Hepatic Impairment

Non-liposomal vincristine sulfate is excreted primarily by the liver. The influence of severe hepatic impairment on the safety and efficacy of Marqibo has not been evaluated.

The pharmacokinetics of Marqibo was evaluated in patients with moderate hepatic dysfunction (Child-Pugh B) secondary to melanoma liver metastases. The dose-adjusted maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of Marqibo in patients with moderate hepatic impairment was comparable to the C_{max} and AUC of patients with ALL who had otherwise normal hepatic function.

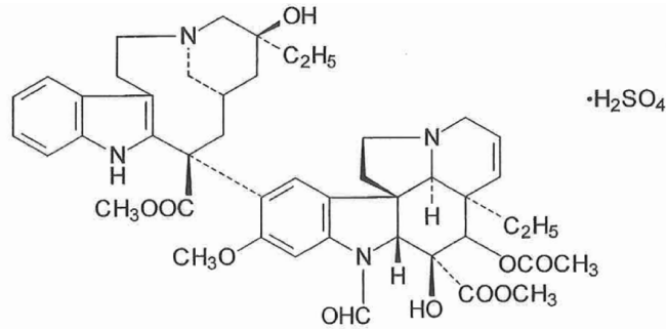
10 OVERDOSAGE

When Marqibo (vinCRIStine sulfate LIPOSOME injection) was administered at a dose of 2.4 mg/m^2, severe toxicities including motor neuropathy of Grade 3, grand mal seizure of Grade 4, and elevated aspartate aminotransferase and hyperbilirubinemia of Grade 4 were reported in 1 patient each. There is no known antidote for overdosage.

11 DESCRIPTION

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

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 $C_{46}H_{56}N_4O_{10} \bullet H_2SO_4$. The chemical name for vincristine sulfate is 22-oxovincaleukoblastine 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, 36 mg sodium citrate, 38 mg citric acid, 355 mg sodium phosphate, and 225 mg sodium chloride.

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1.14 Labeling

Marqibo (vinCRIStine 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 (vinCRIStine sulfate LIPOSOME injection) include:

- VinCRIStine Sulfate Injection, USP (5 mg/5 mL). Each VinCRIStine Sulfate Injection vial consists of 5 mg/5 mL vincristine sulfate (which is equivalent to 4.5 mg/5 mL vincristine free base) and 100 mg/5 mL mannitol.
- 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 plasma pharmacokinetics of Marqibo was investigated in 13 adult patients with relapsed ALL who received a Marqibo dose of 2.25 mg/m^2 administered as a 1-hour intravenous infusion. The calculated pharmacokinetic parameters for total plasma vincristine sulfate are given in Table 3. The vincristine sulfate levels reported in Table 3 reflect liposome-encapsulated drug that may not be immediately bioavailable and may not be 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 Treated with 2.25 mg/m^2 Marqibo[a]

Variable	N	Mean	SE	Median	Range
AUC_∞ (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.

The plasma clearance (CL) of Marqibo is slow, 345 mL/h, at a dose of 2.25 mg/m^2. This is in comparison to the rapid clearance of non-liposomal vincristine sulfate at 189 mL/min/m^2 (11,340 mL/h). The slow clearance of Marqibo contributes to a much higher AUC for Marqibo relative to non-liposomal vincristine sulfate.

Reference ID: 3172211

Following intravenous administration of Marqibo, urinary excretion was a minor route of elimination for vincristine sulfate and its metabolite. Less than 8% of the administered Marqibo dose was eliminated in urine over a 96-hour observation period, which is similar to the urinary excretion of non-liposomal vincristine sulfate. Following non-liposomal vincristine sulfate infusion, the main route of vincristine sulfate excretion was the fecal route, accounting for 69% of the administered dose over 72 hours.

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 some *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 causes testicular degeneration and atrophy, and epididymal aspermia in rats.

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.

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/m^2/week and included uncoordinated movements, weakness, reduced muscle tone, and limited usage of the limbs. Neurological testing indicated drug-induced peripheral neurotoxicity with both drugs. Based on the histopathology examination after 6 weekly doses, 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. In a separate tissue distribution study in rats, administration of 2 mg/m^2 of intravenous liposomal or non-liposomal vincristine sulfate showed greater accumulation of vincristine sulfate in sciatic and tibial nerves (as well as the lymph nodes, spleen, and bone marrow) of the animals following vincristine sulfate liposome injection.

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/m^2 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. NIOSH Alert: Preventing occupational exposure to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193.
4. Polovich M, White JM, Kelleher LO (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

The Marqibo Kit (NDC # 20536-322-01) contains:

- Vial containing VinCRIStine Sulfate Injection, USP 5 mg/5 mL (1 mg/mL) – NDC # 20536-323-01
- Vial containing Sphingomyelin/Cholesterol Liposome Injection 103 mg/mL – NDC # 20536-324-01
- Vial containing Sodium Phosphate Injection 355 mg/25 mL (14.2 mg/mL) – NDC # 20536-325-01
- 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

Reference ID: 3172211

16.1 Storage

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

17 PATIENT COUNSELING INFORMATION

Physicians 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)*].

Ability to Drive or Operate Machinery or Impairment of Mental Ability: 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)*].

Gastrointestinal/Constipation: 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, such as docusate. Instruct patients to seek medical advice if they experience symptoms of constipation such bowel movement infrequency, abdominal pain, bloating, diarrhea, nausea, or vomiting [*see Warnings and Precautions (5.6)*].

Pregnancy/Nursing: Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with Marqibo [*see Warnings and Precautions (5.9)*]. Instruct patients to report pregnancy to their physicians immediately. Advise patients that they should not receive Marqibo while pregnant or breastfeeding. If a patient wishes to re-start breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician [*see Use in Specific Populations (8.3)*].

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking [*see Drug Interactions (7)*].

Peripheral Neuropathy: Advise patients to contact their physicians 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)*].

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

Manufactured by:

VinCRIStine Sulfate Injection, USP
Hospira Australia Pty Ltd
Mulgrave, Victoria 3170
Australia

Sphingomyelin/Cholesterol Liposome Injection
Cangene Corporation
Winnipeg, Manitoba R3T 5Y3
Canada

Sodium Phosphate Injection
Jubilant HollisterStier
Spokane, WA 99207

Marqibo Kit for the Preparation of vinCRIStine sulfate LIPOSOME injection
Anderson Packaging, Inc
Rockford, IL 61109

Distributed by:

Talon Therapeutics, Inc.
400 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Patient Information
Marqibo® (mar-KEY-bo)
(vinCRIStine sulfate LIPOSOME injection)

Read this Patient Information before you begin receiving Marqibo® and before each Marqibo infusion. There may be new information. This information does not take the place of you talking with your doctor about your medical condition or treatment.

What is Marqibo

Marqibo is a prescription medicine used to treat adults with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) when:

- their leukemia has come back (relapsed) after 2 or more anti-leukemia therapies, **or**
- their leukemia became worse (progressed) after two or more anti-leukemia therapies.

It is not known if Marqibo is safe and effective in children or in elderly adults.

Do not receive Marqibo:

- if you have certain conditions of the brain or spinal cord, including Charcot-Marie-Tooth syndrome. Talk to your doctor before receiving Marqibo if you have a condition that affects your brain or spinal cord.
- if you are allergic to vincristine sulfate or any of the ingredients in Marqibo. See end of this leaflet for a list of the ingredients in Marqibo.
- as an injection into your spine (intrathecal). Marqibo causes death if given by any route other than by intravenous (IV) infusion.

What should I tell my doctor before receiving Marqibo?

Before receiving Marqibo, tell your doctor if you:

- have had treatment containing vincristine sulfate in the past
- currently have numbness or tingling in your feet or hands or decreased sensitivity to heat, cold, or pain
- have difficulty walking or picking up and holding items with your hands
- have a change in bowel regularity or constipation, and difficulty passing urine
- have head or jaw pain
- have liver problems
- are pregnant or plan to become pregnant. Marqibo can harm your unborn baby. You should not become pregnant while taking Marqibo. Use an effective method of birth control during treatment with Marqibo. Tell your doctor right away if you become pregnant while taking Marqibo.

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- are breastfeeding or plan to breastfeed. It is not known if Marqibo passes into your milk. You and your doctor should decide whether you will take Marqibo or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Marqibo may affect the way other medicines work, and other medicines may affect how Marqibo works.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Marqibo?

- You will receive Marqibo as an intravenous (IV) infusion in your vein over 1 hour. Marqibo is usually given every 7 days.
- Your doctor may change your dose, give you Marqibo less often, or stop your treatment with Marqibo if you have certain side effects.
- Your doctor should do blood tests regularly to check for side effects of Marqibo.

What should I avoid while receiving Marqibo?

- Marqibo can cause tiredness (fatigue) and nerve problems (neuropathy). You should not drive or operate machinery if you develop any of these symptoms. See "What are the possible side effects of Marqibo?"

What are the possible side effects of Marqibo?

Marqibo can cause serious side effects, including:

- **Tissue injury.** If Marqibo leaks from your vein into the tissues around your intravenous (IV) line, it can cause damage to those tissues. **Tell your doctor or nurse right away if you develop burning, redness or swelling at your IV site during or after your infusion.**
- **Nerve problems (neuropathy).** Nerve problems are common with Marqibo and may get worse over time. Your doctor may need to change your dose, or delay or stop your treatment with Marqibo if you develop nerve problems. Symptoms may include:
    - numbness and tingling, or burning in your feet or hands
    - increased or decreased feeling of sensation to pain, touch, heat, or cold in your feet or hands
    - joint and muscle pain
    - pain in your jaw or head
    - muscle spasms
    - weakness in the hands or feet

Reference ID: 3172211

    - dizziness or feel faint when you go from lying down to sitting, or from sitting to standing.
    - trouble picking up or holding items with your hands
    - slapping or dropping of the front part of your foot when walking forward (footdrop)
    - unsteadiness when standing or walking
    - difficulty speaking
    - constipation or a change from the normal regularity of your bowel movements
    - difficulty passing urine
    - difficulty with erection or ejaculation in men

- **Low blood cell counts.** Marqibo may cause you to have low red blood cells (anemia), low white blood cells (neutropenia), and low platelets (thrombocytopenia). Your doctor should do blood tests to check your blood cell counts before each dose of Marqibo. Your doctor may need to change your dose of Marqibo and treat your low blood cell counts if needed. Tell your doctor if you develop fever or cough up phlegm (productive cough).
- **Tumor lysis syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have:
    - kidney failure and the need for dialysis treatment
    - an abnormal heart beat

  Your doctor will check you for TLS during treatment with Marqibo, and treat you for this problem if it happens.
- **Constipation and intestinal (bowel) blockage.** Your doctor will prescribe a bowel regimen for you to help prevent constipation or intestinal blockage. Symptoms may include:
    - stomach area (abdomen) pain, bloating or diarrhea
    - nausea or vomiting
- **Tiredness (fatigue)**. Marqibo can cause severe tiredness or weariness. Your doctor may need to change your dose, or delay or stop you treatment if this happens.
- **Liver problems that can cause death.** Marqibo can cause changes in liver function tests or more serious liver problems that can cause death. Your doctor:
    - will monitor your liver function test during treatment with Marqibo.
    - may change your dose or stop your treatment with Marqibo if you develop liver problems.

Reference ID: 3172211

Common side effects of Marqibo include:

- nausea
- fever
- diarrhea
- decreased appetite
- sleep problems

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effect of Marqibo. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Marqibo

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This leaflet summarizes the most important information you need to know about Marqibo.

If you would like more information about Marqibo, talk with your doctor. You can ask your pharmacist or doctor for information about Marqibo that is written for health professionals. For more information, go to www.MarqiboRX.com or call 1-888-292-9617.

What are the ingredients in Marqibo?

Active ingredient: vincristine sulfate

Inactive ingredients: mannitol, sphingomyelin, cholesterol, sodium citrate, citric acid, sodium phosphate and sodium chloride.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Distributed by:

Talon Therapeutics, Inc.
South San Francisco, CA 94080

Issued August 2012

Reference ID: 3172211

Artwork Proof #__15__

NDC 20536-322-01

Rx only

Marqibo®

(vinCRIStine sulfate LIPOSOME injection)

5 mg/31 mL (0.16 mg/mL)

For Intravenous Use Only
Fatal If Given By Other Routes

Must be diluted prior to administration

Single Use Vial – Discard Unused Portion

Patient ID: _____

Date: _____

Heat at 63°C to 67°C for 10 min.

Temp In: _____

Time In: _____

Temp Out: _____

Time Out: _____

Kit Lot#

(01)00320536322019

Read package insert before use.

Administer diluted Marqibo® within 12 hours of preparation start time.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

DO NOT FREEZE.

Talon Therapeutics, Inc.
South San Francisco, CA 94080

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Marqibo®

(vinCRIStine 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

N 3 20536-322-01 9

NDC 20536-322-01

Rx only

Marqibo®

(vinCRIStine 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
- VinCRIStine 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 Unsued Portion

LOT/EXP AREA

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Marqibo®

(vinCRIStine 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

VinCRIStine Sulfate Injection, USP Ingredients:
vincristine sulfate, USP, mannitol, USP, water for injection, USP

Marqibo Kit Ingredients:
5 mg vincristine sulfate, 500 mg mannitol, 73.5 mg sphingomyelin, 29.5 mg cholesterol, 36 mg sodium citrate, 38 mg citric acid, 355 mg sodium phosphate, and 225 mg sodium chloride.

For Intravenous Use Only
Fatal If Given By Other Routes

Mfg. for:
Talon Therapeutics, Inc.
South San Francisco, CA 94080

Pkgd. by:
AndersonBrecon, Inc.
Rockford, IL 61109

(b) (4)

Reference ID: 3172211

Artwork Proof #__12__

NDC 20536-325-01

Rx only

Sodium Phosphate Injection 355 mg/25 mL (14.2 mg/mL)

for use only in the preparation of **Marqibo®**

Single Use Vial – Discard Unused Portion
See package insert for preparation instructions

Mfg. for: Talon Therapeutics, Inc., South San Francisco, CA 94080
Mfg. by: Jubilant HollisterStier, Spokane, WA 99207

Store at 2°C to 8°C
(36°F to 46°F)
DO NOT FREEZE.

(01)00320536325010

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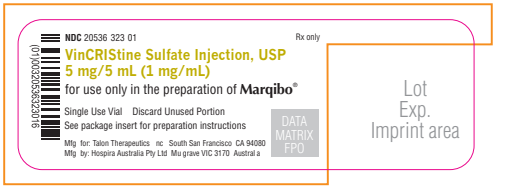

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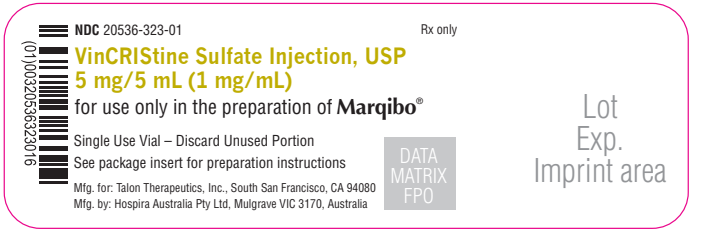

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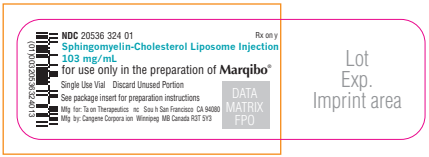

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Marqibo®

(vinCRISTine sulfate LIPOSOME injection)
(diluted)

For Intravenous Use Only
Fatal If Given By Other Routes

Invert 5 times immediately prior to infusion

Patient ID: _____

Treatment dose _____ mg Marqibo®

Administer diluted Marqibo® at a controlled infusion rate over 60 minutes.

Expiration Date and Time: _____

Must complete administration by the expiration date and time.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F). **DO NOT FREEZE.**

Do not mix with other drugs or bacteriostatic agents.

DATA MATRIX FPO

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Reference ID: 3172211

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/s/

ANN T FARRELL
08/09/2012