

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Options Review

Date: June 29, 2012

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Drug Name(s): Marqibo (vincristine sulfate liposomal injection)

Therapeutic Class: Vinca alkaloid antineoplastic

Dosage and Route: 2.25 mg/m² intravenously every 7 days

Application Type/Number: NDA 202497

Submission Number: Risk Management Plan, July 12, 2011, submitted with
original application

Applicant/sponsor: Talon Therapeutics, Inc.

OSE RCM #: 2011-3509

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EXECUTIVE SUMMARY

Marqibo (vincristine sulfate liposomal injection) is under consideration for the treatment of Philadelphia Chromosome-negative (Ph-) Acute Lymphoblastic Leukemia (ALL) in adult patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. The liposomal formulation was developed to decrease neurotoxicity (the dose-limiting toxicity) with vincristine, thus allowing administration of higher doses of vincristine than can be achieved with vincristine sulfate. However, in pre-clinical testing in rats, signs of neurotoxicity were greater with the vincristine sulfate liposome injection compared to the non-liposomal vincristine. The single-arm clinical trial did not permit a direct comparison to vincristine at the same dose in patients. The number of patients requiring neuropathy-related dose reduction, dose delay, and missed doses suggested to the FDA clinical reviewer that Marqibo does not have a better neurotoxicity profile than vincristine¹.

The preparation of Marqibo for administration to the patient is complex. Marqibo is prepared from the components in the Marqibo kit which includes separate vials of sphingomyelin/cholesterol liposomes, vincristine sulfate, and sodium phosphate. Preparation of a Marqibo dose requires combining the appropriate amounts of sphingomyelin/cholesterol liposomes, vincristine sulfate, and sodium phosphate and then heating the combined ingredients in a water bath at 63°-65°C for 10 minutes. After heating, the constituted drug is allowed to cool to room temperature, and then the patient-appropriate amount of product is added to an infusion bag of 5% dextrose injection or 0.9% sodium chloride injection to a total volume of 100 mL.

The potential harm to patients with improper preparation of Marqibo is not clear. Although the complicated dose preparation appears to be unprecedented with an FDA-approved drug, the applicant stated that there were no reports of errors were associated with drug preparation in clinical testing. At this time, we are not able to characterize with certainty the potential harm to patients that could be associated with errors in preparation of the product. Infection from contamination of the product during preparation and neurotoxicity from failure to encapsulate vincristine are possible outcomes.

It is not clear that there is a role for a risk evaluation and mitigation strategy (REMS) for Marqibo. The instructions for preparation in the labeling should be improved and clearly state what to do when deviations in preparation occur. A postmarketing requirement (PMR) should be sought to survey users of Marqibo regarding difficulty they have in preparing doses of Marqibo for administration.

1 INTRODUCTION

1.1 BACKGROUND

Marqibo is under consideration for the treatment of Ph- ALL in adult patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. The liposomal formulation was developed to decrease neurotoxicity (the dose-

¹ Dr. Ashkan Emadi, April 17, 2012 Clinical Review of NDA 202497

limiting toxicity) with vincristine, thus allowing administration of higher doses of vincristine than can be achieved with vincristine sulfate. Standard vincristine is dosed 1.4 mg/m², while Marqibo's proposed dose is 2.25 mg/m².

Marqibo was studied in 65 patients in a Phase 2, international, multicenter, open-label, single-arm trial in patients with Ph- ALL or lymphoblastic lymphoma in second or greater relapse, or with disease that had failed two or more anti-leukemia therapies, and who were ineligible for hematopoietic stem cell transplantation. FDA review of the response of patients showed that 10 of the 65 patients experienced a complete remission or complete remission with incomplete blood count recovery. Five of 8 of these patients had durations of response of less than one month. The median duration of response was 28 days. Twelve of the patients received hematopoietic stem cell transplantation subsequent to treatment with Marqibo. Five patients in the study lived longer than a year after enrollment in the study. According to the FDA review of the data, the role of Marqibo in the survival of the patients who survived longer than one year was questionable.

Preparation of Marqibo doses requires combining the appropriate amounts of sphingomyelin/cholesterol liposomes, vincristine sulfate, and sodium phosphate (the ingredients are available separately in a kit), and then heating the combined ingredients in a water bath at 63°-65°C for 10 minutes. After heating, the constituted drug is allowed to cool to room temperature, and then the patient-appropriate amount of product is added to an infusion bag of 5% dextrose injection or 0.9% sodium chloride injection to a total volume of 100mL. The drug is then infused into the patient over 60 minutes.

1.2 REGULATORY HISTORY

In March 2004, a previous applicant submitted an application under the 21 CFR 314.500, Subpart H, for Marqibo for the treatment of aggressive or refractory non-Hodgkin's Lymphoma. A non-approvable action was taken on this application in January 2005. The reasons cited in the letter included lack of evidence showing improvement over available therapy, and Chemistry, Manufacturing, and Controls (CMC) deficiencies. Concerns about the potential for error in preparing the doses, raised in a November 2004 review by the Division of Medication Errors and Technical Support (DMETS), were not included in the action letter.

In July 2011, Talon Therapeutics submitted the current application for the treatment of Philadelphia Chromosome-negative (Ph-) Acute Lymphoblastic Leukemia (ALL) in adult patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. The application was considered at a meeting of the Oncology Drugs Advisory Committee (ODAC) March 21, 2012. ODAC recommended approval of the application (vote 7-4 with 2 abstentions).

1.3 PRODUCT LABELING

The proposed labeling includes instructions for preparing the dose using the contents of a Marqibo kit. The kit contains 1 vial vincristine sulfate injection 5 mg/5mL, 1 vial sphingomyelin/cholesterol liposomes injection (102 mg/mL), 1 vial sodium phosphate injection (14.2 mg/mL), 1 flotation ring, 1 Marqibo overlabel to be used during preparation, 1 infusion bag label, and 1 package insert label. Using these ingredients and

a water bath and calibrated thermometer, personnel are to follow the (b) (4)-step instructions in the proposed labeling to prepare the dose. This process requires combining the ingredients, heating the combined ingredients, removing the heated product from the water bath, allowing the heated product to cool to ambient temperature, withdrawing the patient-specific dose and injecting the dose into an infusion bag of 5% dextrose injection or 0.9% sodium chloride injection to a total volume of 100mL. The drug is then infused into the patient over 60 minutes.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

We reviewed the following:

- November 30, 2004 DMETS Final Proprietary Name Review; this review contained comments regarding concern about preparing the dosage form
- Non-approvable action letter for Marqibo NDA 21-600 issued January 14, 2005 to Inex Pharmaceuticals
- Proposed labeling submitted with the July 2011 NDA submission
- Proposed Risk Management Plan submitted with the July 2011 NDA submission
- FDA Briefing Document for the March 21, 2012 ODAC meeting
- April 17, 2012 Clinical Review of NDA 202497
- The applicant's April 19, 2012 response to the March 28, 2012 Information Request
- April 25, 2012 Cross-Discipline Team Leader Review of NDA 202497
- The applicant's April 28, 2012 email response (received April 30, 2012) answering Agency questions regarding how the product was prepared in clinical testing
- McCune JS, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm.* 1997; 54:1755-8

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Marqibo was studied in 83 patients in two trials, including an 18-patient supportive study and the pivotal trial of 65 patients. The pivotal study in 65 patients was a Phase 2, international, multicenter, open-label, single-arm trial in patients with Ph- ALL or lymphoblastic lymphoma in second or greater relapse, or with disease that had failed two or more anti-leukemia therapies, and who were ineligible for hematopoietic stem cell transplantation. FDA review of the response of patients showed that 10 of the 65 patients experienced a complete remission or complete remission with incomplete blood count recovery. Five of these patients had durations of response of less than one month. The median duration of response was 28 days.

The following table from Dr. Qin Ryan’s review of the application presents the efficacy results from the study, based on the reviews of Dr. Emadi (clinical reviewer) and Dr. Huang (statistical reviewer).

Efficacy Results from Phase 2 Clinical Trial of Marqibo

RESPONSE	Trial HSB (N=65)
Complete remission (CR), n (%)	3 (4.6)
CR with incomplete blood count recovery (CRi), n (%)	7 (10.8)
CR + CRi, n (%) (95% CI ^a)	10 (5.4) (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 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 HSCT (n=10)	56 (9, 65)

a CI = Confidence interval (Clopper-Pearson)
Source: Reviews of Drs. Emadi and Huang.

Twelve of the patients received hematopoietic stem cell transplantation subsequent to treatment with Marqibo. Five patients in the study lived longer than a year after enrollment in the study. According to Dr. Emadi’s review of the data, the role of Marqibo in the survival of the patients who survived longer than one year was questionable.

3.2 SAFETY CONCERNS

In clinical testing, adverse events were observed in 100% of patients and adverse events > Grade 3 were reported in 96% of patients. The most common adverse events (>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%).

3.2.1 Microbial or Fungal Contamination

Infectious adverse events occurred in 33 (39.8%) patients. Due to their disease state, patients in the trial were at increased risk for infection, and there is no indication that contaminated product caused any of the infectious events. Nevertheless, the preparation of doses of Marqibo requires multiple steps and manipulation of the product that could result in microbial or fungal contamination.

3.2.2 Neurotoxicity

Seventy-two of the 83 patients (86.7%) reported neuropathy-related adverse events. Twenty-seven of the neuropathy-related adverse events were grade 3 or more in severity. Peripheral neuropathy leading to treatment discontinuation occurred in 10% of patients in the Marqibo clinical trials. Neuropathy events leading to discontinuation of Marqibo included decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain (one event each).

Six of 83 patients missed doses in the clinical trials because of neuropathy including peripheral neuropathy, pain in extremities, facial neuralgia, and ileus.

The single-arm trial did not permit a direct comparison to vincristine at the same dose. The number of patients requiring neuropathy-related dose reduction, dose delay, and missed doses suggests that Marqibo does not have a better neuropathic toxicity profile than vincristine, in the assessment of the FDA clinical reviewer.

3.3 APPLICANT’S PROPOSAL FOR RISK MANAGEMENT

The applicant did not propose a REMS for Marqibo. The applicant identified neuropathy, neutropenia, secondary infections, and unidentified possible effects specific to liposomal formulation, and unidentified risks associated with extravasation as the most important risks to consider for risk mitigation. The applicant assessed that these risks can be managed with product labeling and routine pharmacovigilance.

The applicant assessed the potential for medication errors with Marqibo. The applicant argued that the preparation and administration of Marqibo by healthcare professional staff using the instructions in the product labeling make errors unlikely. Regarding the potential for product confusion between the liposomal formulation of vincristine and standard vincristine, the applicant believes that the name “Marqibo” is sufficiently distinctive to prevent confusion. They stated that they did not identify any medication errors during product development. The applicant did not include the potential for medication errors as a risk to consider for risk mitigation.

3.3.1 Proposed Postmarketing Studies

The applicant has proposed a phase 3, multicenter, randomized, confirmatory study of Marqibo compared with standard vincristine in the treatment of patients with newly diagnosed acute lymphoblastic leukemia. The primary endpoint is overall survival, and the proposed sample size is 348. Potential study sites are being evaluated currently, and three sites were open to enrollment as of March 2012.

4 DISCUSSION

Consideration of REMS under FDAAA

The Food and Drug Administration Amendments Act (FDAAA) of 2007 requires that the Agency consider six factors in determining whether a REMS is needed for a given product. These factors are: the estimated size of the population likely to use the drug involved, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug with respect to such disease or condition, the expected or actual duration of treatment with the drug, the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity. After considering these factors, a REMS should be instituted for a product if the REMS is needed to ensure that the benefits of the product outweigh its risks.

The data for the six factors for Marqibo are detailed below.

- The estimated size of the population likely to use the drug involved.
The following figure, from Dr. Emadi's clinical review of the application, illustrates that about 450 patients yearly would be eligible for use of Marqibo.

Adult Patients with Ph- ALL in the U.S.

Copyright Material



Thomas et al. 1999, Tavernier et al. 2007, O'Brien et al. 2008

- The seriousness of the disease or condition that is to be treated with the drug.
 - Patients with relapsed ALL have a poor prognosis.
- The expected benefit of the drug with respect to such disease or condition.
 - Ten of the 65 patients studied experienced a complete remission or complete remission with incomplete blood count recovery.
- The expected or actual duration of treatment with the drug.
 - Patients are treated with Marqibo until disease progression or unacceptable toxicity occurs. The median duration of response in patients studied was 28 (range, 7 to 36) days.
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
 - Peripheral neurotoxicity is the dose-limiting side effect of vincristine. Most patients with ALL treated with vincristine experience peripheral neurotoxicity.
- Whether the drug is a new molecular entity (NME).
 - Marqibo is not an NME.

According to the clinical review, the risk–benefit assessment for Marqibo only marginally favors approval. Marqibo was tested in an open-label single-arm trial. Although the applicant believes Marqibo has an advantage in tolerability, this benefit has not been established in a clinical trial. The risk–benefit of Marqibo was considered by ODAC, and the committee recommended approval.

Preparing Marqibo for Administration

The main concern regarding the use of Marqibo resides in the complicated preparation of each dose using the product kit. Although perhaps not unusual for a research facility, preparation of a dose in the manner described is not usually performed in outpatient practices or even within most hospital pharmacies. The kit contains 1 vial vincristine sulfate injection 5 mg/5 mL, 1 vial sphingomyelin/cholesterol liposomes injection (102 mg/mL), 1 vial sodium phosphate injection (14.2 mg/mL), 1 flotation ring, 1 Marqibo overlabel to be used during preparation, 1 infusion bag label, and 1 package insert label. Using these ingredients and a water bath and calibrated thermometer, personnel are to follow the (b) (4)-step instructions in the proposed labeling to prepare the dose. This process requires combining the ingredients, heating the combined ingredients, removing the heated product from the water bath, allowing the heated product to cool to ambient temperature, withdrawing the patient-specific dose and injecting the dose into an infusion bag of 5% dextrose injection or 0.9% sodium chloride injection to a total volume of 100 mL. The drug is then infused into the patient over 60 minutes.

During preparation of the dose, while the combined ingredients are being heated in the water bath, the preparer must monitor the calibrated thermometer nearly continuously to be sure that temperature excursions outside a narrow range do not occur. Should temperature excursions outside a narrow range occur, the vincristine might not be encapsulated within the liposomes.

Preparation of the dose requires the preparer to move the vial and ingredients in and out of the clean room. First, the preparer must combine the ingredients in a biologic safety cabinet within the clean room. After combining the ingredients, the preparer must remove the vial containing the combined ingredients from the biologic safety cabinet in the clean room and take the vial to the ante room for heating in the water bath. After heating and allowing the product to cool to ambient temperature, the vial is returned to the biologic safety cabinet in the clean room to remove the dose from the vial and inject it into an infusion bag.

Failure to prepare the Marqibo dose correctly might result in failure to encapsulate the vincristine within the liposomes. The patient would then receive an infusion of Marqibo containing higher amounts of free vincristine than anticipated. Failure to maintain sterility throughout the preparation process could result in microbial or fungal contamination of the product.

Risk of Bacterial or Fungal Contamination

The draft labeling requires administration within 12 hours of beginning the preparation of the dose. The risk of causing bacterial or fungal illness from product contamination

during preparation is low if the product is administered within 12 hours of beginning preparation.

Risk of Neurotoxicity

Data submitted by the applicant show that a 10-minute constitution time at 62°C to 68°C results in acceptable encapsulation of vincristine. It is not clear what the risk to patient is if temperature in the water bath is outside the acceptable range and the vincristine is not encapsulated. While oncology practitioners generally use a maximum single dose of 2 mg of standard vincristine, there are not strong data in the medical literature supporting this maximum single dose. The data do not establish a maximum single or cumulative dose^{2,3}. Therefore, we do not know the extent of the risk to patients should encapsulation fail.

REMS Considerations

Based on the proposed indication, it is likely that most patients would receive treatment with Marqibo in a comprehensive cancer center. It is not known whether practice settings without the appropriate facilities for preparation of Marqibo will use the product. Ideally, practice sites will assess their own capabilities and facilities, and they will not use the product if they do not have the personnel or facilities to prepare Marqibo. Outpatient use of Marqibo would be discouraged as well by the lack of insurance reimbursement for the lengthy preparation process.

We considered whether a REMS with required training of hospital pharmacists and hospital pharmacy technicians should be instituted. The value of individual certification is questionable because the patient population is very small, and it is likely that trained personnel would prepare Marqibo infrequently. Trained personnel would not retain preparation skills if long periods of time elapse between episodes of preparation of the product. They would thus need to be retrained frequently or trained immediately prior to the preparation of the next dose after a period of months has elapsed between training and preparation or between preparation of doses. It would be difficult for hospital pharmacies to ensure that all possible preparers (all staff, all shifts) of Marqibo are trained and to ensure that certified preparers are available to prepare Marqibo at any time that the product could be ordered.

To better understand practitioner experience in preparing Marqibo, we talked to a senior pharmacist at the National Institute of Health (NIH) Clinical Center in Bethesda, Maryland, about their experience preparing Marqibo. They believed that the preparation was reasonable as long as very detailed directions for preparation are included in the labeling, the preparer did not have to do anything else while it was being prepared, and if the labeling included information about what to do in various scenarios (temperature excursions etc) that could reasonably be expected to occur during the preparation of the doses. The NIH pharmacy technicians who have prepared Marqibo did not think the preparation was difficult, although the preparation was lengthy, and the preparation

² Haim N, Epelbaum R, Ben-Shahar M, et al. Full dose vincristine (without 2-mg dose limit) in the treatment of lymphomas. *Cancer*. 1994;73:2515-9.

³ McCune J, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm*. 1997;54:1755-8.

required close attention. They also believed that it would be advisable to limit preparation of Marqibo to times that are well-staffed with both pharmacy and nursing staff; that is, during weekday day-shift. Although the NIH tries to prepare Marqibo during times of best staffing, they acknowledged that it is not always possible to do so.

The most important factors to ensuring proper preparation of Marqibo are ensuring that hospital pharmacies have the materials required for the preparation (water bath, thermometer), and clear, explicit instructions for preparation. These can be provided outside a REMS. It is not clear what additional margin of safety might be provided by instituting a REMS to limit preparation to trained hospital pharmacists and hospital pharmacy technicians.

5 CONCLUSION

Because the preparation for administration of Marqibo is complex, the potential for medication errors exists. However, the risk to patients associated with errors in the preparation of Marqibo is not well characterized. Therefore it is reasonable to manage the risks of Marqibo with labeling, pharmacovigilance, and surveillance of practice settings to determine if the practice settings are experiencing difficulty with preparation of the product. A PMR should be sought to periodically survey users of Marqibo about difficulties they have experienced preparing doses of Marqibo.

The instructions for preparation in the Marqibo labeling should be improved to include the following:

- 1) Clarify that the 12-hour product expiration clock for the product begins when preparation begins
- 2) Directions for preparation using closed system transfer devices (e.g., PhaSeal)
- 3) Movement of the product in and out of the biologic safety cabinet and in and out of the clean room
- 4) Placement of the water bath
- 5) The preparer should monitor the temperature of the water bath continuously during heating of the product
- 6) Action to take for temperature excursions
- 7) The preparer of Marqibo doses should not attempt to perform any other tasks while Marqibo is being prepared
- 8) Action to take in the case of equipment (water bath, thermometer) failures

The applicant should be encouraged to reformulate this product into a ready-to-use product.

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