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DRUG DISCOVERY

FDA Approval for Vincristine Sulfate Liposome

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1. INTRODUCTION

On August 9, 2012, the Food and Drug Administration (FDA) granted accelerated approval for vincristine sulfate liposome injection (Marqibo®, made by Talon Therapeutics, Inc.) 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. The approval is based on the rate of complete remission (CR) plus the rate of complete remission with incomplete blood count recovery (CRi) in a single-arm, single-agent trial of 65 adults in second or greater relapse.

2. CHARACTERISTIC FEATURE OF MORQIBO (BRAND NAME)

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.

3. VINCRISTINE SULFATE LIPOSOME INJECTION

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 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 $C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$. The chemical name for vincristine sulfate is 22-oxovincaleukoblastine and it has the following chemical structure:

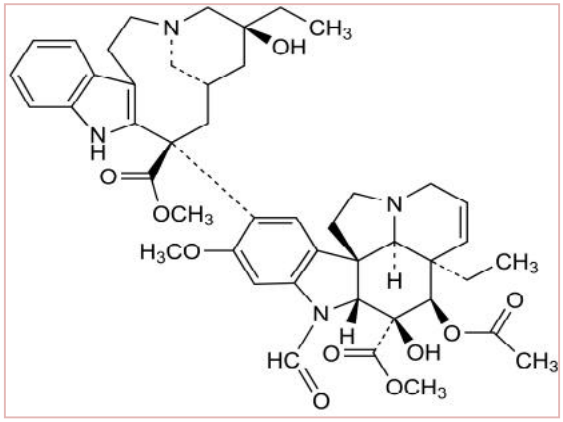
Vincristine is encapsulated in a Sphingomyelin/Cholesterol liposome. The lipid components in the liposome are sphingomyelin and cholesterol at a molar ratio of approximately 60:40 (mol:mol). After preparation, each vial of Marqibo contains 5 mg vincristine sulfate, 500 mg mannitol, 73.5 mg sphingomyelin, 29.5 mg cholesterol, 36 mg sodium citrate, 38 mg citric acid, 355 mg sodium phosphate, and 225 mg sodium chloride.

4. PREPARATION OF MARQIBO VIAL

Preparations 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.

5. PRECLINICAL AND CLINICAL STUDIES



Preclinical and clinical studies showed that liposomal encapsulation of vincristine sulfate (VCR) results in increased drug circulation time and accumulation of VCR at the tumor site. Marqibo has been administered safely at 2.25 mg/m2, a dose exceeding that typically employed for VCR (dose capped at 2 mg), with tolerable clinical toxicities consistent with VCR. Of the 27 previously treated patients with metastatic melanoma in the Marqibo pharmacokinetic studies, 3 patients had a tumor response, including one patient with uveal melanoma metastatic to the lung that experienced a complete response. Methods: Patients with metastatic uveal melanoma with no more than one prior systemic therapy were enrolled. Patients with controlled brain metastases were allowed. Marqibo (2.25 mg/m2 by 1-hour intravenous infusion, no dose capping) was administered every 14 days until tumor progression. Responses were assessed every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST). Toxicity was assessed at least as frequently as before each dose. Results: Preliminary data is available for 22 enrolled patients (73% female). Median age was 65 years (range 38-79), 23% were previously treated with systemic chemotherapy, 86% had liver metastasis and 96% had M1c disease. Baseline serum LDH levels were elevated in 73% and were more than 2 x ULN in 37% of the patients. Twenty-one patients were evaluable for response; one patient discontinued the treatment after a single dose of

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therapy for toxicity without tumor progression. No patients died of drug toxicity while on the study. Twelve patients (57%) had stable disease. Estimated median survival is 6.4 months. Fourteen patients are alive, 2 for more than 12 months. Treatment related side effects were mostly grade 1 or 2; peripheral neuropathy was the only grade 3 toxicity, seen in 18% of the patients. The hematologic toxicities were minor; no neutropenia or thrombocytopenia was seen. Conclusions: Marqibo is well tolerated as single agent therapy in patients with advanced stage IV uveal melanoma. Its impact on the progression-free and overall survival of these critically ill patients will be presented.

6. EFFICACY

The efficacy of vincristine sulfate liposome was studied in the HBS407 trial, which enrolled patients age 18 years or older with Philadelphia chromosome-negative ALL in second or greater relapse or whose disease progressed after two or more anti-leukemia treatment regimens. Patients had to have achieved a CR from one of the prior anti-leukemia chemotherapies, defined by a leukemia-free interval of at least 90 days. At the time of screening and enrollment, patients had to be ineligible for immediate hematopoietic stem cell transplantation. All patients had received prior vincristine sulfate; 22 (34 percent) had not received asparaginase products. The safety of vincristine sulfate liposome at the dose of 2.25 mg/m^2 weekly was evaluated in HBS407 and VSLI-06 (an earlier phase I/II trial) that included a total of 83 patients with ALL in second or greater relapse. Adverse reactions were observed in 100 percent of patients. The most common adverse reactions (more than 30 percent) were constipation, nausea, pyrexia, fatigue, peripheral neuropathy, febrile neutropenia, diarrhea, anemia, decreased appetite, and insomnia. Severe adverse reactions occurred in 96 percent of patients. The most common infections were: neuropathy, febrile neutropenia, neutropenia, anemia, and thrombocytopenia. Deaths occurred in 23 percent of patients in the HBS407 trial. Causes of death were brain infarct, intracerebral hemorrhage, liver failure, multi system organ failure, pneumonia and septic shock, respiratory failure, pulmonary hemorrhage, and sudden cardiac death.

7. MODE OF ACTION

Marqibo contains the chemotherapy drug vincristine, which interferes with the ability of cancer cells to divide. The vincrist ine is encased in material (a liposome) that helps to deliver the drug to cancer cells. It is given as an intravenous (into a vein) infusion.

8. SIDE EFFECTS

Common side effects include: Nausea, Fever, Diarrhea, Decreased appetite, Sleep problems. Some of the potentially serious side effects include: Tissue injury (if the drug leaks out of the vein and into surrounding tissues), Nerve problems (neuropathy), Low blood cell counts, Tumor lysis syndrome (a condition caused by the fast breakdown of cancer cells; it may cause kidney or heart problems), Constipation and intestinal blockage, Severe fatigue and Liver problems. Some patients may experience other side effects that are not listed here. Some side effects may require medic al attention. Other side effects do not require medical attention and may go away during treatment. Patients should check with their physician about any side effects that continue.

9. HOW TO PREVENT DISCOMFORT AND SIDE EFFECTS

- Pay careful attention to the physician's instructions and inform the physician of any side effects.
- Maintain adequate rest and nutrition.
- If possible, avoid large crowds or people who are sick or not feeling well, as this drug may leave some patients susceptible to infection.
- Wash hands often to reduce the risk of infection.
- Eat small meals frequently to help alleviate nausea.
- Avoid activities that may cause injury or bruising.
- Use a soft toothbrush and an electric razor to prevent cuts on the mouth or skin.

10. SPECIAL PRECAUTIONS BEFORE STARTING TREATMENT

- Patients should inform their physician of any other medication they are taking (whether prescription or over-the-counter, including vitamins, herbs, etc.) as they may interact with treatment.
- Patients should inform their physician about any past treatment with vincristine.
- Patients should inform their physician if they are pregnant, breastfeeding or planning a family in the near future.
- Patients should inform their physician about all medical conditions, including liver problems; conditions that involve the brain or spinal cord; numbness or tingling in the hands or feet; decreased sensitivity to heat, cold, or pain; bowel or urinary problems; head or jaw pain; or difficulty walking or picking up and holding items.
- Patients should inform their physician about prior allergic reactions.

11. CONCLUSION

The prescribing physician is solely responsible for making all decisions relating to appropriate patient care including, but not limited to, drugs, regimens, dose, schedule, and any supportive care.

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