CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202497Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	202497
Applicant Name	Talon Pharmaceuticals, Inc.
Date of Submission	July 13, 2012
PDUFA Goal Date	August 13, 2012
Proprietary Name / **Established (USAN) Name**	Marqibo kit – to administer Vincristine in a liposomal formulation
Dosage Forms / Strength	kit
Proposed Indication(s)	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 treatment lines of anti-leukemia therapy.
Action/Recommended Action for NME:	**Accelerated Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Ashkan Emadi, M.D./ Qin Ryan, M.D., PhD.
Statistical Review	Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Stacey Ricci, MEng, ScD./ Haleh Saber, Ph.D.
CMC Review/OBP Review	Xiao Chen, Ph.D./Janice Brown, M.S./Sarah Pope Miksinski, Ph.D. and John Duan, Ph.D./Angelica Dorantes, Ph.D.
Microbiology Review	Vinayak B. Pawar, Ph.D./J. Metcalfe, Ph.D.
Clinical Pharmacology Review	Bahru Habtemariam Pharm.D./ Julie Bullock, Pharm.D.
DDMAC	
DSI	Anthony Orencia, M.D.
CDTL Review	Qin Ryan, M.D., Ph.D.
OSE/DMEPA	Jibril Abdus-Samad, Pharm. D./ Todd Bridges, Pharm.D./Carol Holquist, R. Ph.
OSE/DDRE	
OSE/DSRCS	
Other -MHT	

Signatory Authority Review Template

1. Introduction

NDA 202497 is a 505 b2 application for Marqibo kit. Marqibo kit is comprised of three vials (vincristine sulfate, liposomes (sphingomyelin/cholesterol liposome) and sodium phosphate injection), labels and a floatation ring. This drug product is notable for being prepared/manufactured at the pharmacy instead of at a commercial site. This product is intended to be used as monotherapy to treat 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 treatment lines of anti-leukemia therapy.

This NDA was submitted to the Agency on July 13, 2012. The Agency filed the application and granted a standard review with a PDUFA goal date of May 14, 2012. During the review cycle a number of CMC and Microbiology deficiencies were identified. The Agency sent these deficiencies in an Information Request letter. The Applicant responded with a major amendment extending the PDUFA clock until August 12, 2012.

Talon's Marqibo is not marketed in any country or region.

2. Background

Marqibo is a kit containing 3 vials that will be mixed at a pharmacy site. The final product is the liposomal formulation.

The kit contains the following:
*1 vial **Sodium Phosphate Injection** (14.2 mg/mL) to be used as constitution vial*

*1 vial **Sphingomyelin/Cholesterol Liposomes Injection** (103 mg/mL)*

*1 vial **Vincristine Sulfate Injection, USP** (5 mg/5 mL)*

1 Flotation Ring

1 Marqibo (vincristine sulfate liposomes injection) Overlabel for Sodium Phosphate Injection Constitution Vial

1 Infusion Bag Label

1 Package Insert label

3. CMC/Device

From the CMC primary review of the original submission dated 4/13/12:

*From a CMC perspective, this application is recommended for a **Complete Response** action. The following issues need to be completely resolved before this NDA can be recommended for approval. 1) An overall acceptable recommendation from the Office of Compliance; 2) Satisfactorily resolving the CMC deficiencies listed as follows;*
1. The requested VSI impurity profile comparison between your VSI lots and RLD was not provided in the Amendment (SN0009) dated February 13, 2012. Provide full comparative data for the complete impurity profiles of the proposed VSI formulation (at least 3 lots) and the reference listed drug, i.e. list all individual related substances with their RRTs (relative retention time).
2. Regarding the VSI OOS results at the accelerated conditions at 3 and 6 months, although you provided up to 2 months stability data (one month data for 3 lots and two months data for 1 lot) at the accelerated conditions of 25°C/60% RH in the amendment, you did not provide the shipping conditions, such as duration and temperature.
Therefore, you did not adequately address the concern regarding two months stability data at 25°C/60% RH being sufficient to support the shipping and handling conditions for both VSI and VSLI.
3. Include the proposed acceptance limit for unspecified degradation products of no more than (b) (4) *in the table for SCLI specification.*
4. You have stated that vincristine sulfate is a natural product that is one of the over 70-member vinca alkaloid chemical family isolated from the periwinkle plant Catharanthus roseus (Madagascar periwinkle). Provide the source of the raw material, the periwinkle plant, and indicate whether it is grown as a wild plant or cultivated plant. If it is a wild grown plant, you will need to file an Environmental Assessment (EA). If it is cultivated non-wild grown plant, you may claim categorically exclusion under 21 CFR 25.31(a) and/or 21 CFR 25.31 (c). Please refer to the attached FDA document regarding EA Review Requirements for Drugs Derived from Plant Sources.

An Information Request letter was sent asking the Applicant to address these issues. The Applicant responded with a major amendment which was reviewed by the CMC review team.

In their review of the major amendment they have the following recommendations:

From a CMC perspective, this application is recommended for approval provided that an overall "Acceptable" EES recommendation and an "Acceptable" recommendation from microbiology review are provided. All CMC review deficiencies/comments have been satisfactorily addressed. The container carton labeling and the proposed Package Insert are still under review and revision.

Also note that the Microbiology review is still pending, an overall recommendation regarding approvability has not been issued from a Microbiology standpoint, and final labeling is still pending.

Dr. Chen's review states the following regarding expiry and stability:

The shelf life of VSLI is determined in such a way that shortest expiry of all three components will be the expiration date for VSLI. A 24-month shelf life for the Marqibo VSLI kit stored at 5°C protected from light (VSLI is light sensitive) was proposed and is found to be acceptable based on the stability data generated for each individual component of the kit and those of VSLI. An in-use stability study was conducted that demonstrated the diluted drug is physico-chemically stable for 12 hours when stored at 5 to 25°C in the dark or in typical room light.

Based on the stability data provided, the proposed expiry of 24 months stored at 36-46^{o}F (2-8^{o}C) is acceptable.

4. Nonclinical Pharmacology/Toxicology

Talon references data from Oncovin NDA on the genotoxicity/mutagenicity potential of vincristine sulfate as part of the reproductive toxicity assessment of Marqibo.

The nonclinical review team relied on published literature and the Oncovin label. Thus this application is a 505 b2.

No issues that would preclude approval were identified. The secondary non-clinical pharmacology/toxicology review for this application noted that this application relied on published literature to address non-clinical sections of the labeling.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified.

From the Clinical Pharmacology Review:

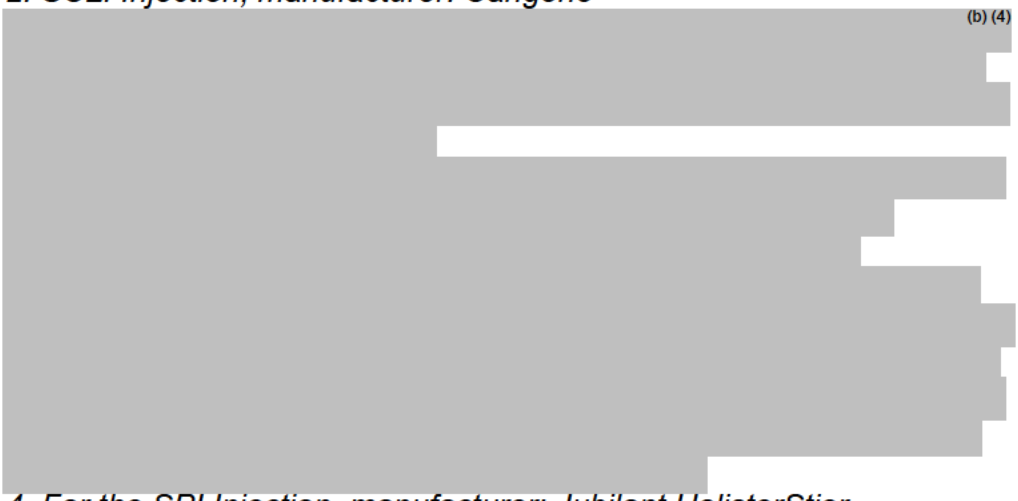
Pharmacokinetic data were available from seven patients with moderate (n=6) and severe (n=1) hepatic impairment, which were compared to the PK of patients with normal hepatic function who took part in a separate study. The Cmax and AUC of patients with moderate hepatic impairment were similar to those with normal hepatic function that took part in the pivotal study.

6. Microbiology

Based on the original submission, the Microbiology review team did not recommend approval. The language reproduced below is from the pages of their original review:

From the review:
Drug Product Marquibo® was submitted under NDA 21-600 by Tekmira Pharmaceuticals and received a non approval action in 2005. Talon addressed Quality and other issues from the Agency's enquiry and claims there are no outstanding issues from NDA 21-600 non approval letter that would prevent submission and acceptance for filing NDA 202497. The applicant is seeking accelerated registration of Marquibo® vincristine sulfate liposomes Injection through the electronic submission of this original NDA 202497. IQA was filed by CMC on 09/06/2011. On February 9, 2012 an IR was sent to the sponsor to request information on the aseptic handling of the Marquibo® kit during reconstitution in a pharmacy setting and to justify the post constitution storage of 12 hours through the absence of microbial growth. The justification for post constitution storage of 12 hours was provided on March 23, 2012. Information on aseptic handling of the Marquibo® kit during reconstitution in a pharmacy setting is pending to this date.

Deficiencies identified by the review team:
1. For the constitution of the Marquibo kit, the contents of three separate vials will be combined in the VSLI vial, heated at 65 + 2oC in a water bath for the eventual administration of the admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. What precautions will be taken to ensure that aseptic conditions will be maintained throughout the constitution process, in a pharmacy setting?
2. SCLI Injection, manufacturer: Cangene



4. For the SPI Injection, manufacturer: Jubilant HolisterStier

An Information Request letter was sent asking the Applicant to address these issues. The Applicant responded with a major amendment addressing these issues.

The Microbiology team reviewed the major amendment and recommends approval as of July 25, 2012.

7. Clinical/Statistical-Efficacy

From the primary reviewer's review:

NDA 202497 submission is seeking accelerated approval for Marqibo for the treatment of adult (age >18 years) patients with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. Marqibo is administered at a dose of 2.25 mg/m$_2$ IV every 7 days as a 60 minute infusion for a 28-day course of treatment. The clinical evidence of safety and efficacy to support this claim was based on a single arm trial.

This reviewer acknowledges that the decision on recommendation on regulatory action for this NDA is not straightforward. However, based on following discussion and risk benefit assessment, this reviewer recommends accelerated approval of Marqibo for the proposed indication with implementation of postmarket requirement to be performed with due diligence with respect to the conduct of the confirmatory study. This recommendation was based on
• a 15% CR+CRi rate
• a median CR+CRi duration of 28 days between two confirmed CR or CRi and 56 days from the first documented CR or CRi until the next therapy including HSCT
• an 8% subsequent stem cell transplant rate after achievement of CR or CRi after single agent Marqibo
• a reasonable safety profile which does not appear to be different than vincristine based on the literature

I concur with the clinical and statistical reviews for this product.

8. Safety

No unique safety issues have been identified which distinguish this product from vincristine sulfate which is not liposomal-encapsulated. However, this conclusion has limitations based on the fact that most of the data on safety derives from small single agent/arm trials.

The following text is from the medical officer's primary review:

Regarding the risks, due to lack of randomized study comparing Marqibo to vincristine, it is difficult to support any advantage in safety of Marqibo without a direct comparison to vincristine. Applicant's claim of the better tolerability of Marqibo

compared to vincristine can be questioned by 21% missed doses, 22% dose reduction and the fact that 30% of patients completed cycle 2, and only 5% completed cycle 3. A total of 96% of patients had an adverse event of Grade 3 or higher, 76% of patients reported serious AEs, 29% of patients had AEs with outcome of death and 28% had AEs leading to discontinuation. Moreover, with regard to neuropathy, 87% of patients reported neuropathy of any grade, 33% reported neuropathy related AEs of grade 3 or higher which impair activities of daily living, 13% had a serious adverse event of neuropathy,and 10% discontinued study treatment due to peripheral neuropathy. Although, these adverse events are important and non-negligible and they don't support advantage over other cytotoxic chemotherapies in general and vincristine in particular, they are considered common and manageable by most oncologists who treat acute leukemias especially in patients whose disease relapsed after first or second lines of therapy.

9. Advisory Committee Meeting

This application was presented at an ODAC meeting on March 21, 2012. The following question was asked: Has Marqibo demonstrated a favorable risk-benefit for the treatment of adult patients with Philadelphia chromosome negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy?

The vote was mixed with 7 yes, 4 no and 2 abstain. During the meeting a number of issues were raised including the feasibility of their proposed confirmatory study in patients 60 years and older. The endpoint of the trial will be overall survival. Some of the concerns arose from the fact that one of the Applicant's consultants questioned the use of L-asparginase in older patients with ALL.

The Applicant discussed the feasibility of this study with the review team in a meeting on April 2, 2012. The Applicant proposed amendments to the ongoing trial which the applicant believes will facilitate enrollment and address feasibility issues: lowering the age for eligibility and increasing the number of recruitment sites.

10. Pediatrics

This product has Orphan designation. The sponsor plans to conduct pediatric studies.

11. Other Relevant Regulatory Issues

From the Office of Scientific Investigations review:
Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

Because the approval is under Subpart H (Accelerated Approval), the Applicant will be required to confirm clinical benefit. The Applicant has proposed that their ongoing

phase 3 trial to compare standard vincristine sulfate injection with Marqibo as used in combination chemotherapy for the treatment of patients with newly diagnosed acute lymphoblastic leukemia. This trial if successful could be used for conversion to full approval. During the Advisory Committee meeting, several ODAC members raised questions about feasibility. The Applicant does not believe feasibility will be an issue and discussed this concern with the Division on April 2, 2012.

The Office of Surveillance and Epidemiology Division of Medication Error Prevention and Analysis was concerned about numerous safety issues regarding the preparation/manufacturing of Marqibo and the labeling instructions. Staff concerns were addressed through labeling and post-marketing commitments. The following text is from the executive summary which summarizes their major concerns:

DMEPA has been concerned with the overall product design and proposed product preparation procedures for Marqibo since our first consultation in 2003. Due to the following medication error concerns, we requested a product redesign prior to approval.
The proposed product requires encapsulation of vincristine into liposomes and the concentration of free vincristine is critically dependent upon the accurate preparation of this liposomal formulation. Specifically, deviating from the specified procedures regarding the time and temperature ranges required during preparation would result in decreased encapsulation of vincristine and therefore considerably more free vincristine in solution. This represents a critical safety concern as the dosing and administration for the liposomal formulation is dependent upon the near complete encapsulation of vincristine. The greater amount of free vincristine may cause a serious risk to patients because the liposomal formulation is dosed considerably higher than the non-liposomal formulation of vincristine.
Moreover, the equipment required to prepare Marqibo including a hot water bath, calibrated thermometer, and timer are not typically available in inpatient pharmacies, outpatient chemotherapy centers, or general oncology practices….

These issues have been addressed during post-ODAC negotiations and in labeling. The text is from their review:

- *Provide recommendations for the placement, use, and cleaning of the water bath*
- *Provide recommendations regarding movement of the vial in and out of the sterile field and how to maintain sterility for the final drug preparation in IV bag*
- *Include information from clinical trials that Marqibo preparation required a dedicated person to monitor temperature and time accurately and to prevent distractions*
- *Provide information that encapsulation of vincristine into the liposome is time and temperature dependent.*
- *Provide directions for when deviations outside the temperature and time parameters occur during preparation.*
- *Provide advice regarding how to handle equipment failure.*

Additionally DMEPA negotiated post-marketing commitments with the applicant. The following is text from their review:

Postmarketing commitment to explore other design options to simplify preparation of Marqibo, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated and to survey pharmacies in order to obtain post-marketing experience from facilities that use this product. This data will be used to monitor for any difficulties and medication errors due to the unusual preparation of this product. Knowledge gained from this survey may also provide insight to improve the instructions for use in the labeling.

12. Labeling

All disciplines made recommendations for labeling which were incorporated into labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Accelerated Approval

- Risk Benefit Assessment
  In the single arm clinical trials conducted, Marqibo kit produces responses including complete responses with a minimum duration of 28-56 days with an acceptable toxicity profile. However, the responses do not provide evidence of clinical benefit. Therefore the applicant will have to conduct a randomized clinical trial to provide evidence of clinical benefit.The applicant has proposed that the following study will provide the evidence:

  A Phase 3, Multicenter, Randomized Study to Evaluate the Substitution of Marqibo (vincristine sulfate liposomes injection, VSLI) for Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Subjects ≥ 60 Years Old with Newly diagnosed Acute Lymphoblastic Leukemia

  This trial if successful could be used for conversion to full approval.

- Recommendation for Post marketing Risk Management Activities
  Routine pharmacovigilance

- Recommendation for other Post marketing Study Requirements/ Commitments

  Due to the complexity of the manufacture/preparation, the applicant has agreed:

  to study and report at 6 month intervals on the experience of health care practitioners regarding any safety or technical problems with the preparation of Marqibo.

  to consider ways to simplify the preparation of Marqibo by eliminating any unnecessary steps

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/s/

ANN T FARRELL
08/09/2012