

Division Director Summary Review

NDA: 50-718/S-033

Drug: DOXIL® (doxorubicin HCL liposome injection) for intravenous infusion

Applicant: Johnson and Johnson Pharmaceutical Research and Development, LLC

Date: June 10, 2008

This supplement requests conversion of the following indication from accelerated approval to full approval: “DOXIL is indicated for the treatment of AIDS-related Kaposi’s sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.” The NDA was originally approved on 11/17/95 under the accelerated approval regulations. Study 30-38B was conducted as the confirmatory trial and the results were originally submitted in [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

This submission provides data from an additional cooperative group study, E1D96, as well as literature that supports the efficacy of DOXIL in patients on stable doses of highly-active antiretroviral therapy (HAART). The results from the two studies are summarized in the following excerpt from the package insert.

Retrospective efficacy analyses were performed on two studies that had subsets of patients who received single agent DOXIL and who were on stable antiretroviral therapy for at least 60 days prior to enrollment and at least until a response was demonstrated. In one cooperative group trial that was closed early due to slow accrual, 7 of 17 patients (40%) on stable antiretroviral therapy had a durable response. The median duration was not reached but was longer than 11.6 months. In another trial, 4 of 11 patients (40%) on stable antiretroviral therapy demonstrated durable responses.

The safety profile in these studies was similar to that in the approved label.

### Clinical/Statistical Review

The joint Clinical/Statistical Review of 6/3/08 made the following recommendations on regulatory action and risk benefit assessment.

#### **1.1 Recommendation on Regulatory Action**

Doxil was approved on November 17, 1995 pursuant to 21 CFR 314.510 (accelerated approval) “for the treatment of AIDS-related Kaposi’s sarcoma (AIDS-KS) in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.”

This review recommends conversion of accelerated to regular approval for the above indication based on the sNDA reviewed in this documentation and the reasons outline in the section 1.2.

#### **1.2 Risk Benefit Assessment**

This recommendation is based on totality of data.

a. Clinical evidences supports that Doxil is active in AIDS-KS. Response as a single agent or in comparison to effective treatments, such as single agents of DaunoXone (study 30-38B) and paclitaxel (ECOG E1D96), combination therapy of ABV (adriamycin + bleomycin + vincristine, published literature) and BV (bleomycin + vincristine, published literature). This includes durable responses (40%) observed in Studies 30-38B and ECOG E1D96 in KS patients in whom the results were not confounded by changes in highly-active antiretroviral treatment (HAART). Although the sample size of the subgroup of patients on stable HAART patients is small (n=11 in study 30-38B and n=17 in E1D96), the effect is consistent across both studies.

b. Based on the published literature, although HAART is an important component of treatment for all patients with AIDS-KS, there is scant evidence that HAART induces regression of advanced, symptomatic AIDS-KS without concomitant anti-KS therapy. Confounding by concomitant treatment with HAART and decreased incidence of KS in the HAART era has made adequate enrollment in to clinical trials difficult in a disease that remains as the most common malignancy in AIDS patients.

c. Thirteen years after the initial accelerate approval of Doxil in 1995 for treatment of AIDS KS patients; its safety profile has been well documented and established. No new safety issue identified in this review.

The safety of Doxil is well-known and is the risk-benefit ration is acceptable.

There were no recommendations for postmarketing risk management activities or new postmarketing study commitments.

### Clinical Team Leader's Review

The Clinical Team Leader's Review of 6/6/08 made the following recommendation.

This NDA should be approved for conversion of the accelerated approval granted in year 1995 for the following indication:

*“DOXIL is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.”*

This recommendation is based on totality of data. This includes durable responses (40%) observed in Studies 30-38 and ECOG E1D96 in KS patients in whom the results were not confounded by changes in highly-active antiretroviral treatment (HAART). Although the sample size of the non-confounded patients is small (n=11 in study 30-38B and n=17 in E1D96), it is consistent across both studies. These results are supported by published literature. Confounding by changes in HAART and decreased incidence in the HAART era has made adequate enrollment in to clinical trials difficult in a disease that remains as the most common malignancy in AIDS patients.

The safety of DOXIL is well-known and is the risk-benefit ratio is acceptable.

### Conclusion

I concur with the recommendations of the clinical and statistical review teams. Although the size of the database is small, the objective response rates were approximately 40% in two studies which enrolled patients on stable HAART. These response rates and the durations of the responses are clinically meaningful. These results are also supported by the literature summarized in the Clinical Review. I also agree that the safety profile of DOXIL is well-established and that the risk-benefit ratio is acceptable.

Robert L. Justice, M.D., M.S.  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Office of New Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert Justice  
6/10/2008 07:59:59 PM  
MEDICAL OFFICER