

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

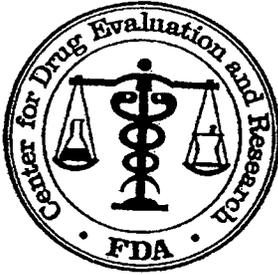
APPLICATION NUMBER:

22-276

MEDICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Clinical and Cross Disciplinary Review



NDA: 22-276
Drug: nicardipine hydrochloride injection
Indication: short-term treatment of hypertension when oral therapy is not feasible or not desirable
Sponsor: Teva Parenteral Medicines, Inc.
Review date: July 23, 2008
Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

Recommendation and Conclusions

I recommend approval of Teva's nicardipine hydrochloride injection for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. All disciplines with submitted data or references to data recommend approval. There are no clinical data submitted or required for this 505(b)(2) application. The one outstanding clinical issue is the potential for venous irritation due to the addition of benzoic acid as an excipient. Until the sponsor submits a clinical venous irritation study documenting low rates of venous irritation I recommend incorporating _____

b(4)

_____ Besides adding the venous irritation warnings and incorporating Dr. Resnick's recommendations regarding labeling changes, we need to revise the innovator's label to be consistent with the Physician Labeling Rule before approving it as Teva's nicardipine hydrochloride injection label.

Materials Used in Review

1. CMC Reviews by Lyudmila N. Soldatova, Ph.D. dated May 6, 2008 and June 4, 2008
2. Microbiology Review by Bryan S. Riley, Ph.D. dated March 25, 2008
3. Pharmacologist's Review by C.A. Resnick, Ph.D. dated March 20, 2008
4. NDA 22-276 submission dated September 28, 2007

Background

Nicardipine hydrochloride injection is a new formulation of an approved product PDL BioPharma's Cardene IV (NDA 19-734). We required the sponsor to submit a 505(b)(2) application rather than an ANDA because we judged the formulation changes, benzoic acid replacing citric acid monohydrate _____ and sodium chloride replacing sorbitol _____, to be unacceptable for an ANDA. One issue is that the excipient benzoic acid has been associated with venous irritation in IV solutions of other marketed drugs, e.g., diazepam (Valium).

b(4)

Chemistry, Manufacturing, and Controls (CMC)

The CMC reviewer, Dr. Soldatova, recommends approval from the CMC standpoint. The drug substance and drug product manufacturing facilities were found acceptable according to the overall OC recommendation on March 20, 2008. Based on the provided stability data, Dr. Soldatova recommends a nine-month expiry for the drug product.

Microbiology

The microbiology reviewer Dr. Riley recommends approval from the standpoint of product quality microbiology. He summarizes that the drug product is _____
_____ He does not note any microbiology deficiencies.

b(4)

Nonclinical Pharmacology and Toxicology

The nonclinical pharmacology reviewer Dr. Resnick recommends that the application is approvable from the perspective of pharmacology. He notes that no nonclinical safety data were provided with this submission but that it relies upon the prior approval of the innovator Cardene. He has recommendations for changing the proposed labeling, and that of the innovator and any other generics, _____

b(4)

Clinical

There are no clinical or clinical pharmacology data provided in this submission. As an IV solution issues of bioavailability or bioequivalence are not applicable. For substantial evidence of safety and efficacy we are depending upon our findings of safety and efficacy for Cardene, NDA 19-374, which has no remaining exclusivity or patent protection.

The one clinical issue that we have discussed with the sponsor is the potential for venous irritation because of the addition of benzoic acid as an excipient. Valium IV has 5% sodium benzoate and benzoic acid as buffers. Rates of venous irritation are reported as about 20% for valium IV but less than 2% for Cardene IV. We have proposed including the statements regarding venous irritation _____ in Teva's nifedipine label.

b(4)

The concentration of benzoic acid in Teva's formulation is 0.03% and is further diluted 1:25, with a suitable diluent, prior to infusion. The sponsor argues that, because of the lower concentration, venous irritation should not be problematic. While the sponsor's argument is not without merit, we require that lack of venous irritation be demonstrated in an adequate and well-controlled trial. _____

b(4)

Regarding special populations, the sponsor requested a waiver of pediatric studies. However, our pediatric team determined that, because there is no change in active ingredient, indication, dosage form, dosing regimen, or route of administration, pediatric

studies are not required by PREA and hence a waiver is not applicable. Note also the changes to labeling recommended by Dr. Resnick ~~_____~~
Otherwise, there are no new clinical data regarding special populations.

b(4)

There are no other clinical issues for this drug. Except perhaps for the potential for venous irritation, I would expect it to perform virtually identical to the innovator. Any issues regarding its approvability are related to the CMC, microbiology, and nonclinical pharmacology issues I summarized above.

**Appears This Way
On Original**

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

/s/

Thomas Marciniak
7/23/2008 12:37:22 PM
MEDICAL OFFICER