CENTER FOR DRUG EVALUATION AND RESARCH

Application Number 75-108

MEDICAL REVIEW(S)

ANDA

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MEDICAL OFFICER REVIEW
May 21, 1998

ANDA 75-108

Product: Nifedipine Extended Release Tablets, 30 mg (future plans 60 mg, 90 mg)

Sponsor: Mylan Pharmaceuticals, Inc.

Inactive Ingredients: PEG), Xanthum Gum and Locust Bean Gum

This consultation was conducted by the Division of Cardio-Renal Drug Products. Review of several chronic toxicity studies which calculated the no-observable-adverse-effects levels for PEG 4000 (the molecular weight of PEG is within that of PEG 4000 and therefore similar adverse events expected), Xanthum gum and Locust Bean gum were found to provide large safety margins for use in humans (90 mg tablets). These were PEG (1111X), Xanthum gum (185X) and Locust Bean gum (73X).

However, increased maternal mortality was found in the Locust Bean gum mouse teratology study. The sponsor attributed this to differences in administration of the gum in the different studies. The Locust Bean gum was given in regular feeds in the other studies but administered, mixed with corn oil to increase dispersion, via gavage tube to the pregnant mice. The Division of Cardio-Renal Drug Products requested that a limited confirmatory animal study be done to confirm the safety of Locust Bean gum in pregnant animals. In this study, pregnant mice received Locust Bean gum in regular feeds. No mortality or adverse events were seen after 20 day dosing with 4500mg/kg/day. The calculated safety margin for 135 mg of Locust Bean gum, present in 90 mg tablets of Nifedipine was found to be high at 1667X.

The Division of Cardio-Renal Drug Products has concluded that all three of these inactive ingredients are safe and have an adequate safety margin as determined by the chronic toxicity studies conducted in animals.

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Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs