DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW
Not Approvable Letter Response

NDA: 21-359

Name of Drug: nitroglycerin ointment 0.4%
Trade Name: Cellegesic
Formulation: ointment
Related Application:

Proposed Indications: relief of pain of anal fissure
Sponsor/Monitors: Cellegy Pharmaceuticals Inc.

Date of Submission: 4/14/05
Date Received by FDA: 4/15/05
Date Assigned: 4/19/05
Date Review Completed: 5/26/05
Reviewer: Thomas A. Marciniak, M.D.

Background:
This review critiques the sponsor's response to a not approvable letter for Cellegesic ointment. An NDA for Cellegesic for anal fissure was submitted in June 2004 and granted a priority review. A not approvable letter was sent to the sponsor on December 23, 2004. The Division discussed the issues with the sponsor at a meeting on March 28, 2005. This submission provides additional analyses based on the discussion at the meeting.

Not Approvable Letter Response:
The following analyses are presented in this response:

- Study 3 (CP125) was re-analyzed using a generalized mixed effects regression model with random intercept and linear time trend using all "relevant" data (no imputation by last-observation-carried-forward [LOCF] and no post-continuation data.) By this there was a statistically significant difference in the primary endpoint ($p<0.0309$).

- A mixed-effects regression analysis using all available data from each subject (i.e., without LOCF imputation and post-discontinuation data) was performed using analgesic use (yes/no) as a time varying covariate, treatment, time, and treatment by time interaction The outcome measure was 24 hour average pain through day 21. Analgesic use was not a

significant covariate ($p<0.53$). Treatment by time interaction remained significant ($p<0.032$).

- The data from all three trials were combined and subset into quintiles by baseline 24 hour average pain score. The 24 hour average pain scores at day 15 (maximal response) and day 21 were computed by quintile and treatment group. The drug/placebo group difference was greatest in quintile 4, 30-50% lower in quintile 5, and negligible in quintiles 1-3 (except in quintile 2 at day 15). Results from study 3 alone are similar.

Comments:
The first re-analysis of the primary endpoint for study 3 is not new. This analysis was also done by the FDA statistical reviewer and presented in his primary review and summarized in my primary review (my Table 25, analysis 7). I see no reason to change my interpretation of this post-hoc analysis discussed in my review. I still argue that by the appropriate, pre-specified analysis of this study the study failed.

Given that study 3 has failed for its primary endpoint, the analysis regarding analgesic use is interesting but not supportive by itself of approval. This analysis suggests that if there is a difference in pain, it is probably not related to analgesic use. The fundamental issue is that the data do not confirm conclusively that there is a difference in pain by treatment group.

The results by baseline pain quintile are not very convincing. If patients with more baseline pain respond better to treatment, why is the response in quintile 4 substantially better than in quintile 5? This analysis is merely hypothesis generating and would have to be confirmed conclusively with a new study.

Recommendations:
The NDA remains not approvable.

Thomas A. Marciniak, M.D.
Acting Deputy Director

cc:

ORIG: NDA 21-359
HFD-110
HFD-110/CSO
HFD-110/TMarciniak

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/s/

Thomas Marciniak
5/26/05 02:20:00 PM
MEDICAL OFFICER