DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 20 December 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

These comments are based on reviews of Drs. Marciniak (clinical; 17 December 2004), Hung (statistics; 17 December 2004), Timmer (chemistry; 13 December 2004), and Proakis (pharmacology). Dr. Beasley (biopharmaceutics; 25 October 2004) issued a memo acknowledging that this resubmission contained no information not previously reviewed. In addition, I have taken into consideration the sponsor's response (14 December 2004) to the Division's discipline review letter of 10 December 2004.

The pertinent regulatory history is that an initial study (study 98-02-01) of efficacy of nitroglycerin ointment was targeted at healing anal fissures. This study was unsuccessful, but the sponsor performed unplanned analyses of anal pain, the results of which encouraged the sponsor to conduct a confirmatory study for anal pain (study 00-02-01). The second study was successful ($p<0.05$) only when a post-hoc analysis different from the one applied to study 98-02-01 was used. The Division appeared to be headed toward an unfavorable regulatory action when the originally submitted NDA was withdrawn by the sponsor. A third study was the subject of a Special Protocol Assessment (1 November 2002) and attendant discussions. The various interactions with the sponsor are summarized in Dr. Marciniak's review.

The sponsor has now resubmitted the NDA with the results of study 03-02-01, and this resubmission has been given a priority review.

The primary end point of study 03-02-01 was the rate of change in anal pain over 21 days. What p-value to assign the results is a matter of some dispute, since, in this small study, the results depend critically upon how a few withdrawn subjects' data are utilized. The sponsor's favorite assessment gives $p=0.0498$, and most other treatments result in larger values, including one apparently most consistent with the protocol which gives $p=0.12$. What is undeniable is that small studies with, at best, marginally significant results are not comforting.

The sponsor cites a meta-analysis of the three studies to obtain $p=0.0007$, but this result is largely the product of the first two retrospective analyses and is not particularly reassuring. I note, too, that as the studies have gotten larger, the magnitude of effects has gone down and the associated p-value has gone up.

The fundamental problem is likely to be that the effect of treatment is very small. By the sponsor's generous interpretation of the findings in 03-02-01, the reduction in anal pain corresponded to a 3-mm shift in the 100-mm VAS for anal pain after 3 weeks of treatment. The placebo effect is 7- to 8-fold larger than this.

This reduction in anal pain is bought at the expense of headache. Follow-up was 100% at 21 days in the placebo group and 90% on nitroglycerin. Five of the 9 withdrawals are attributed to adverse events, the others to patient choice (n=3) or loss to follow-up

(n=1). Ignoring 4 subjects (2 from each arm) from an excluded site, the withdrawal rates at 56 days were 6% on placebo and 14% on nitroglycerin.

The nitroglycerin group had a higher use of concomitant pain medication, chiefly acetaminophen (40% vs 27%), and it is difficult to know whether this alone may account for the small apparent effect on anal pain.

Part of the advice given to the sponsor in discussions of the third study was to use a global pain index, rather than anal pain. Given the marginal overall results and the evident imbalance in headache, it is quite clear that any analysis of global pain would not have favored Cellegesic.

I conclude that the appropriate regulatory action is not approval (NA). These data cannot be made more compelling by further analysis and further study is unlikely to change one's impression of the overall magnitude of effect. If there is an effect of Cellegesic on anal pain, it is too small to be of clinical interest and comes with too high a cost—intolerable headache pain.

I see no evidence in the available data of a greater safety risk associated with the use of nitroglycerin ointment, although, as Dr. Marciniak points out in his review, the available database is pretty small. The sponsor asserts that one can rely upon the safety of nitroglycerin as used in the treatment of angina and myocardial infarction, and this is true, up to a point. However, the different clinical setting is pertinent for at least two reasons. First, the risks may be different. Systemic vasodilation likely contributes to the benefits in angina and myocardial infarction, but it is unlikely to contribute anything but risk in the current setting. Second, the same risks might lead to different risk-benefit decisions in the different clinical settings. The issue of risk is not a significant one in the decision being made here, but the sponsor's assertion that all the required information on safety could be inherited through a 505(b)(2) process is simply untenable.

The sponsor also (14 December 2004) makes reference to the terrible burden of anal pain ("disabling pain", "diminished quality of life", and "[interference] with … daily activities", but the sponsor's development program did not demonstrate effects on any of these things.

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/s/

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