DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 22 December 2004

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

This memo is an addendum to a previous Divisional Memo (20 December 2004), following up on a discussion of review issues with the sponsor (21 December 2004) and a subsequent letter from the sponsor (also 21 December 2004).

The sponsor makes the following points.

(1) *Pain associated with chronic anal fissures is a significant medical problem with currently inadequate medical treatment.* On this point, there is no disagreement.

(2) *The effect of Cellegesic was consistent throughout the development program.* In support of this, the sponsor cites a subject-level pooled analysis of subjects in all three phase-3 studies, with $p<0.0007$. The ISE says this analysis used the same end point as in study 03-02-01, but the letter clarifies that "LOCF was not utilized because NTG-related headaches were not recorded in the first two phase 2 studies." One can see what the effect of such a decision is in the only study in which both analyses are apparently possible—study 03-02-01. Dr. Hung's review describes 7 variations on the primary analysis, including the sponsor's preferred analysis (imputing only for withdrawals for treatment-related headache; $p=0.0498$) and the one I believe is most reasonable and consistent with the protocol (imputing for all headache withdrawals; $p=0.12$), but the very most favorable analysis ($p=0.031$) comes from censoring at the time of withdrawal[1]. There are other reasons to be cautious about interpreting the p-value for this combined analysis. (a) The first two studies were hypothesis-generating. There is no way to control the type-1 error rate for the set of studies by including these data. (b) The results of the three trials get smaller as the studies became larger and the hypothesis became more refined. (c) In the third trial, the disparity in concomitant pain medications can explain the small effect seem. None of these issues are addressed by the sponsor; "$p<0.0007$" greatly exaggerates the degree to which these datasets can be said to tell a consistent tale of benefit.

(3) *The effect of Cellegesic was clinically meaningful.* Establishing an effect (statistical significance on some pre-specified end point) is a necessary but insufficient basis for approval. In this case, the effect is marginally significant and the p-value critically depends on the handling of a few subjects' data. What effect there may be in study 03-02-01 may be attributable to concomitant pain medication, rather than study drug. And what benefit there may be needs to offset headache so severe that it drives subjects out of trials and to offset risks (including those for which the database is too small to address in this patient population) of a variably absorbed and potent vasodilator. The sponsor cites a difference in time to 50% improvement in anal pain as evidence of clinical benefit ("as much as 7 days … through the first

[1] *This result is also noted on page 100 of the sponsor's ISE.*

21 days of treatment"), but this difference is not even nominally statistically significant (p=0.3)[2]. A similar analysis of all three studies is described as nominally statistically significant (p=0.01), but there the nominal effect is only 3 days, and this analysis has same problems as the pooled analysis discussed above.

In summary, the sponsor's arguments do not alter my impression of these data. Whether there is a direct effect of treatment is not clear from study 03-02-01. Viewed most optimistically, the effect is, at best, a small fraction of the placebo effect. I remain of the opinion that these results make this application not approvable.

[2] *And the median difference is only about 2 days.*

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/s/

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MEDICAL OFFICER