DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 23 December 2004

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

This memo is an addendum to two previous Divisional Memos (20 December 2004 and 22 December 2004), following up on an e-mail from the sponsor (22 December 2004).

The sponsor makes the following points.

(1) *Concomitant pain medication was allowed*. On this point, there is no disagreement.

(2) *"Since it was agreed that 8 doses would not confound the results, only those subjects consuming in excess of 8 doses could potentially affect the results."* Had there been a large difference between the treatment groups, one might be able to sustain an argument that differences in ancillary pain medication would have had little impact on the interpretation, but that is not the situation. The effect on anal pain is vanishingly small, and the differences in pain medications are not. Examination of the HEADACHE dataset reveals that, in the first 21 days of treatment, there were 208 episodes of treated headache on placebo and 384 such episodes on nitroglycerin ointment. From the CONMED dataset, 19 subjects on placebo reported use of acetaminophen for any reason in the first 21 days, compared with 30 subjects on nitroglycerin ointment. This certainly could have contributed to the 3-mm difference in the VAS for anal pain.

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.

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/s/

Norman Stockbridge
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MEDICAL OFFICER