CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-156

OFFICE DIRECTOR MEMO

Memorandum

To: Memo to File, NDA 22-156

Subject: NDA 22-156, clevidipine intravenous emulsion (cleviprex, the Medicines Company) for reduction of blood pressure when oral therapy is not feasible or not desirable.

Date: July 28, 2008

Office Director Review: Robert Temple, MD, Dir, ODEI

I. Introduction and Background

Clevidipine is a pharmacologically familiar drug – a dihydropyridine calcium channel blocker (like nifedipine, amlodipine, felodipine and nicardipine, which is also available as an IV form) that is not metabolized by CYP 3A4 (like many of the dihydropyridines) and that has a fairly short half-life (elimination half-life is one hour).

II. Effectiveness (taken from Beasley/Lawrence particularly thorough Clin/Stat review)

The studies most informative about effectiveness were the two ESCAPE studies, ESCAPE-1 in pre-operative patients, ESCAPE-2 in post-operative patients, each of 30 minutes duration. There were also 3 larger, longer (mean 8 hours) comparative studies (ECLIPSE 1-3) in similar settings vs NTG and SNP (pre-operative HT) or nicardipine (post-operative HT), as well as studies in essential HT and severe HT (VELOCITY, uncontrolled). In the ESCAPE and ECLIPSE studies, the doses were titrated, so that D/R and comparative information were hard to assess (if the desired BP was not reached, the dose was simply increased). The ESCAPE, ECLIPSE, and VELOCITY studies include 1846 patients, 992 on clevidipine, 100 on placebo, and 754 on active control.

A. ESCAPE Studies

These were randomized, double-blind, placebo-controlled, multi-center, short (30 minutes to 1 hr) studies in cardiac surgery patients, either pre-operative (ESCAPE-1, BP ≥ 160 mmHg systolic) or post-operative (ESCAPE-2, BP ≥ 140 mmHg systolic). Mean BP's were 178/77 mmHg in ESCAPE-1 and 150/71 mmHg in ESCAPE-2. About half the patients were over 65. The initial dose was about 2 mg/hr, titrated upward (doubled) every 90 sec as tolerated up to 16 mg/hr to achieve goal BP. The primary endpoint in the ESCAPE studies was proportion of patients with "bailout" (premature DC of study infusion within 30 minutes because of lack of effect that demanded treatment, toxicity, or failure to attain a 15% decrease in SBP by 30 minutes).

For ESCAPE 1, 2 combined results were

	Clevidipine n = 114	Placebo n = 101
Success (no bail)	105 (92.1%)	19 (18.8%)
bail out	9 (7.9%)	(81.2%)
safety	3	0
lack of effect or		
treatment failure	9	82

average infusion rate 9.84 mg/hr

Labeling will show actual systolic BP changes in the 2 ESCAPE studies, as shown on p 57 of the Beasley/Lawrence review. The BP curves separated promptly, with a 20 mmHg difference by 5-7 minutes in both studies and a maximum difference of about 35 mmHg (ESCAPE-1) or 25 mmHg (ESCAPE-2). In both studies, about 90% of patients had attained a 15% reduction by 15 minutes.

B. ECLIPSE Studies

These were primarily safety trials; the main effectiveness measure was AUC of the duration of SBP values that were outside a predefined desirable range (65-135 mmHg intra-operative and 75-145 mmHg pre and post-op). The trials were randomized, open-label, active control studies in cardiac surgery patients, with NTG, SNP, and nicardipine as active controls. For pooled data, the percent AUC for SBP outside of range is shown in the following table:

Variable	Clevid	Active	p-value
AUC – SBP outside	22.45	40.41	< 0.001
AUC – SBP above	20.45	36.12	< 0.001
AUC – SBP below	1.99	4.29	0.037

Given the not-very-well-specified ways of using the drugs, one cannot say much more than that clevidipine seemed at least as easy to use as the active controls. The mean duration of use was 8 hours.

III. Safety

A. Clinical

Serious safety endpoints (death, stroke, AMI, and renal dysfunction were examined through day 30 and considered by a blinded Clinical Events Committee. Overall, there were no unexpected serious events attributable to the drug. Review of a placebo (vehicle) and fenoldopam controlled trial, with a non-randomized moxifloxacin arm (QT review of 11/30/07) showed no evidence of QT prolongation, although accounting for heart rate effects was a challenge. There was a transient concern about excess AF in the ECLIPSE studies, but this was resolved.

Deaths occurred in cardiac surgery patients but did not appear attributable to treatment and were similarly distributed among clevidipine and active controls (In ECLIPSE, 21 on clevidipine vs 30 on active controls). Stroke, AMI and renal dysfunction were similarly distributed. SAE's were also similarly distributed and worrisome events (VF, VT, arrest, AMI) were, if anything, more common in some of the active control groups (but all in all, no difference). The rate of hypotension was similar for clevidipine (16.8%) and active comparators (15.5%). Heart rate regularly increases with BP reduction and, if anything, the rate was lower on clevidipine (about 21%) than active comparators (27.5%). A typical increase in HR in the ESCAPE studies was about 10%, in ESCAPE-1, where starting BP was relatively high (> 160 mmHg), and less in ESCAPE-2, where starting BP was lower.

IV. Other Issues

A. Titration

Dr. Beasley felt the rapid titration (q 90 sec) was not really needed and could lead to overshoot. She notes that the full effect of a dose is not seen for 10-15 minutes. The clinical trial results did not really show a problem here and most experience is with the 90 second titration regimen. Labeling states that as goal is approached the time between adjustments should be lengthened to 5-10 minutes. That seems a good compromise between the urgent need to gain BP control and concern with overshoot. Dr. Beasley was also concerned with the recommended use for up to 72 hours, as there were few data past 24 hours. I do not share this concern, given our great familiarity with the drug class and the lack of any better alternative if IV use is still needed.

B. Carcinogenicity/genotoxicity

Clevidipine is metabolized, in part, to formaldehyde, a known genotoxicant (although one we produce ourselves). There are no long-term carcinogenicity studies. It is not clear that clevidipine's genotoxicity (Ames test, moose lymphoma thymidine known locus assay, and chromosomal assay) is fully explained by the formaldehyde, although it appears to account for some of it. This will be noted in labeling but the very short-term use of clevidipine, and widespread exposure to formaldehyde decreases concern here. As Dr. Stockbridge explains; there is general, but not complete agreement, that the very short duration of use and the fact that levels of formaldehyde produced are low compared to our own endogenous production.

V. Conclusion

I concur in the Divisions Approval recommendation