

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-156

SUMMARY REVIEW



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-156 (clevidipine butyrate¹; Cleviprex)

Sponsor: The Medicines Company

Review date: 16 June 2008

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

Distribution: NDA 22-156

DCaRP/Crowley/Beasley/Karkowsky
OB/Lawrence

Clevidipine is a dihydropyridine calcium channel blocker for the _____
_____ t has been evaluated in the pre-, during-, and post-
surgical settings and in patients with mild-to-moderate hypertension. It is not much of
a stretch to extrapolate to severe hypertension.

My review is based upon CMC reviews by Drs. Cooper and Chang (5 March 2008),
microbiology review by Dr. Mello (29 April 2008), pharmacology/toxicology reviews by
Drs. Hausner (11 February 2008 and 27 March 2008) and DeFelice (14 March 2008
and 3 April 2008), medical and statistical review by Drs. Beasley and Lawrence (10
March 2008), clinical pharmacology review by Dr. Velasquez (21 March 2008), and
pharmacometrics review by Dr. Tornoe (30 April 2008). I am generally in agreement
with the summary and points made in the CDTL memo (Karkowsky; 13 May 2008).
Here I highlight only a few issues.

Qualification and limits need to be set for 3 degradants and 2 in-process impurities. In
my view, this is the only issue warranting an approvable action. Drug substance also
requires setting specifications for _____, and impurities.

Based on available empirical data, the microbiology reviewer recommends a 4-hour
lifetime for drug product once the vial's seal has been breached. This will sometimes
necessitate removal of product hung for administration, a safety issue as compliance
cannot be expected to be high.

The review team varies in its level of concern regarding carcinogenic potential. There is
no 2-year carcinogenicity test, as the product was intended for short-term use.
Clevidipine was positive in Ames tests with S9 in three strains, a finding that is perhaps
only partly attributable to the metabolite formaldehyde. However, I find reassurance in
the calculation that the level of formaldehyde produced as a metabolite is small
compared with endogenous production, that the load is rapidly distributed because of
intravenous administration, and—most of all—by the intended short-term use.

The half-life of clevidipine is dominated by distribution, at least early on during
infusion, but the half-life in ex-vivo blood is only 6 minutes and after a 72-hour
infusion this is about what the offset kinetics look like. Dr. Tornoe's PK-PD modeling
was based on the 72-h infusion study in hypertensives. He found that a simple 2-
compartment model was adequate. The exposure-response relationship appears to
follow an E_{max} law peaking at about a 50% reduction in systolic pressure; half of the
maximum effect is achieved with an infusion of about 10 mg/h. There was no loss of

¹ Herein abbreviated to "clevidipine".

effectiveness and no discernible hysteresis observed during and following a 72-h infusion. Dr. Tornoe has modeled these data to obtain a safer and more efficient dosing regimen than the one employed in the clinical trials. This regimen, which has no empirical support, is the one we favor for labeling.

The studies undertaken in the peri-surgical setting employed various positive controls. In this noisy setting, there were no apparent safety issues.

There was no placebo group in the 72-h study of hypertensives. All dose groups (2-16 mg/h) showed some overshoot in blood pressure (5-10 mmHg) above baseline 4-8 hours after the infusion was stopped. This overshoot does not show a clear dose-response and I believe it is not likely to be either real or (if real) of any clinical significance.

Clevidipine is a QT shortener, probably a reflection of inhibiting inward calcium current in the myocardium. In the latter regard, it had effects similar to those of nifedipine.

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/s/

Norman Stockbridge
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MEDICAL OFFICER