CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-500

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-499 (liquid suspension) and 22-500 (tablets)
Clonidine ER for hypertension

Sponsor: Tris Pharma

Review date: 28 November 2009

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

Distribution: NDA 22-499
NDA 22-500
HFD-110/Kozeli

This memo conveys the Division's recommendation to approve extended-release clonidine solution and tablets for treatment of hypertension.

This application has been the subject of reviews of CMC (Mitra 4 September 2009 and 24 November 2009), clinical pharmacology (Kumi 9 September 2009; Madabushi 17 September, 24 November 2009), and medical (Xu 18 November 2009).

Most issues have been addressed in Dr. Targum's CDTL memo (24 November 2009). I summarize very briefly.

All CMC issues have been resolved. There are no outstanding CMC issues.

The liquid suspension and tablet formulations behave similarly, because the extended-release mechanism is———— b(4)

Pharmacokinetic and pharmacodynamic similarity to twice-daily immediate-release clonidine was established through a small study. The Tmax is delayed, but Cmax and AUC meet bioequivalence criteria. Doses of the new formulation of 0.17 and 0.25 mg are equivalent to 0.2 and 0.3 mg of immediate-release tablets.

The formulation shows potential for dose-dumping with ethanol, but the demonstrated effect in 20% ethanol is gradual and only 40% after 3 hours. This is not likely to be clinically relevant.

Clonidine's half-life goes from about 12 hours in normals to about 40 hours in patients in renal failure. Halving the dose in patients with renal failure suffices to compensate for exposure.

All team members concur on approvability.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name	
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE ——— ER ORAL SUSPENSION	b(4
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE ——— ER ORAL TABLETS	b(4

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/s/

NORMAN L STOCKBRIDGE
11/28/2009