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APPLICATION NUMBER:

208686Orig1s000

MEDICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 208686 Enalapril solution (Epaned) for hypertension, heart failure, and left ventricular dysfunction.

Sponsor: Silvergate Pharmaceuticals

Review date: 19 September 2016

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

This memo conveys the Division's decision to approve this application.

This application has been the subject of reviews of CMC (Wilson-Lee et al., 5 August 2016), pharmacology/toxicology (Saulnier; 21 July 2016), and clinical pharmacology (Johannesen; 17 August 2016, 1 September 2016). There is also a CDTL memo (Thompson; 16 September 2016), with which I am in complete agreement.

This is a 505(b)(2) application relying upon safety and effectiveness of Vasotec (NDA 18998). In addition, the application relies upon Silvergate's own NDA 204308 for enalapril powder for oral solution. There are no remaining product quality issues. The facility inspections were waived based on recent inspections for the powder.

There are no new nonclinical studies. Literature suggests irreversible effects on developing kidneys in rodents, although it is not clear to what age these effects correspond in children.

The sponsor performed a bioequivalence study, comparing the oral solution with their powder for oral solution. The review team concluded nonquantitatively that the bioequivalence in this study coupled to the bioequivalence of the powder to Vasotec was acceptable. I concur—although I think we should work out a more formal approach to chains of bioequivalence studies.

Orphan status for pediatric hypertension was granted in 2013 and revoked in April 2016. The Division considers studies of heart failure and left ventricular dysfunction to be impractical in pediatrics, and these are fully waived. Vasotec adequately describes blood pressure effects in children 6-16 years old, but only pharmacokinetics for ages 2 months to 6 years. No pediatric studies are being required.

All of the review team support approval, as do I.

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/s/

NORMAN L STOCKBRIDGE
09/19/2016