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APPLICATION NUMBER:

207620Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM to CLINICAL PHARMACOLOGY REVIEW

NDA Number:	207620
Submission Dates:	December 17, 2014
Submission Type:	Priority
Brand Name:	ENTRESTO®
Generic Name:	LCZ696 (sacubitril/valsartan)
Drug Class:	Angiotensin receptor-Neprilysin Inhibitor
Dosage Form/Route:	Film-coated Tablets/Oral
Dosage Strengths:	50 mg, 100 mg and 200 mg
Proposed Indication:	Treatment of heart failure (NYHA class II – IV) (b) (4)
Proposed Dose:	Target dose is 200 mg twice daily (BID). The starting dose is 100 mg BID. Double dose every 2-4 weeks as tolerated.
Applicant:	Novartis Pharmaceuticals
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewers:	Luning Zhuang, PhD & Sreedharan Sabarinath, PhD
Team Leaders:	Jeffry Florian, PhD & Rajanikanth Madabushi, PhD

INTRODUCTION:

The objectives of this review addendum are:

(1) To compare the mean daily dose of enalapril, the active comparator used in PARADIGM-HF Phase III study, to that in SOLVD-Treatment study (SOLVD-T), and

(2) To document revised estimates for apparent volume of distribution of sacubitril and valsartan.

(1) Mean Daily Dose of Enalapril in PARADIDGM-HF versus SOLVD-T

Background:

In the PRADIGM-HF study, the target dose for enalapril, the active comparator, was 10 mg twice daily (BID). The applicant stated that this target dose was selected because enalapril demonstrated a significant reduction of mortality in SOLVD-Treatment study (SOLVD-T) in patients with NYHA Class II-IV . The reported mean daily dose in all randomized patients for enalapril was 11.2 mg in SOLVD-T. The mean daily dose, among patients on the study medication at final visit, was 16.6 mg in SOLVD-T. In an attempt to compare the dose of enalapril across the two trials, the Applicant computed mean enalapril daily dose from PARADIGM-HF. The mean enalapril daily dose was calculated to be 15.7 mg and 18.9 mg, respectively, in patients who survived to the final visit (i.e., patients who died before their final visits were excluded) and in those patients taking study medication.

The applicant also submitted mean daily dose calculations for enalapril from SOLVD-T. The main assumption for this calculation method was that all mean doses described in the publication were based on the final dose of patients who survived to the final study visit (i.e., patients who died before their final visits were excluded).

The calculations provided by the applicant are listed below:

Methodology of how final mean enalapril doses were calculated in SOLVD-T (From Applicant)

Number of patients randomized to enalapril: 1285

Number of enalapril patients who died before the study final visit: 452

Number of enalapril patients who survived to the final visit: 1285 – 452 = 833

Number of patients who were on enalapril 2.5 mg/d at the final visit: 1.8% × 833 = 15

Number of patients who were on enalapril 5 mg/d at the final visit: 6.7% × 833 = 56

Number of patients who were on enalapril 10 mg/d at the final visit: 9.5% × 833 = 79

Number of patients who were on enalapril 20 mg/d at the final visit: 49.3% × 833 = 411

Number of enalapril patients on study medication at the final visit: 15 + 56 + 79 + 411 = 561

Number of enalapril patients who stopped blinded medication by end of study: 833 – 561 = 272

Final mean daily dose of enalapril:

$$\frac{(15 \times 2.5mg/d) + (56 \times 5mg/d) + (79 \times 10mg/d) + (411 \times 20mg/d) + (272 \times 0mg/d)}{(15 + 56 + 79 + 411 + 272)}$$

$$= \frac{9327.5}{833} = 11.2\ mg/d$$

Mean enalapril daily dose among patients taking study medication:

$$\frac{(15 \times 2.5mg/d) + (56 \times 5mg/d) + (79 \times 10mg/d) + (411 \times 20mg/d)}{(15 + 56 + 79 + 411)} = \frac{9327.5}{561}$$
$$= 16.6\ mg/d$$

Review Team's Comments:

We agree that the proposed calculation method was able to reproduce the reported mean daily dose of enalapril. However, it should be noted that the SOLVD-T publication provided only the percentage of patients at each dose level at the final visit, total number of deaths and the total number of patients who were randomized. It is not clear from the publication whether the percentages of patients at each dose level are based on the overall population or those patients who were alive at the final visit (as proposed by the applicant). The review team tested the alternative assumption i.e., 'all randomized patients' as referring to the overall study population and not just those patients who were alive at the end of the study (See Figure 1 below for a snapshot of the publication). The "final visit" is interpreted as the visit prior to the study end date or the visit prior to an event.

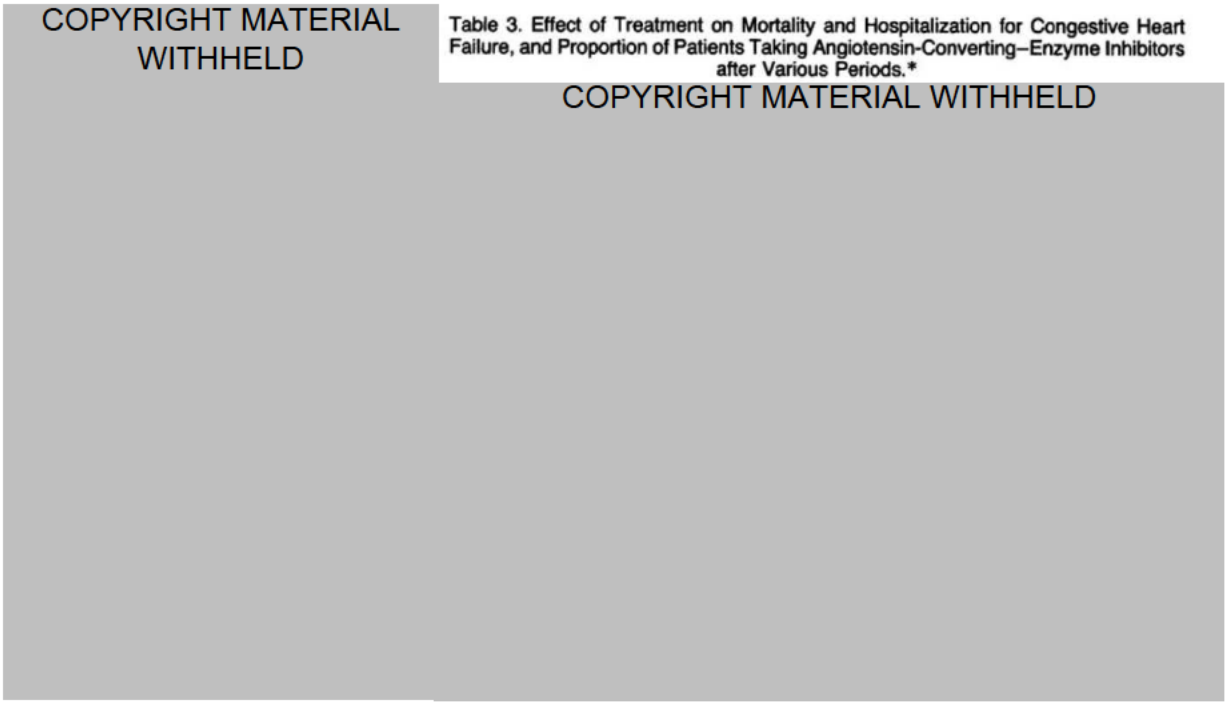

Figure 1. Relevant section of SOLVD-T publication showing mean daily dose of enalapril

Using the same information available from the publication, we can reproduce the reported mean daily dose of enalapril even if we use all patients that are randomized in the SOLVD-T (i.e., using N=1258, without excluding patients who died before final study visit). This is because both calculation methods rely only on the reported percentage of patients at each dose level. Our calculations are illustrated below:

Methodology of how final mean enalapril doses were calculated in SOLVD-T (From FDA)

Number of patients randomized to enalapril: 1285

Number of patients who were on enalapril 2.5 mg/d at the final visit: 1.8% × 1285 = 23

Number of patients who were on enalapril 5 mg/d at the final visit: 6.7% × 1285 = 86

Number of patients who were on enalapril 10 mg/d at the final visit: 9.5% × 1285 = 122

Number of patients who were on enalapril 20 mg/d at the final visit: 49.3% × 1285 =634

Number of enalapril patients on study medication at the final visit: 23 + 86 + 122 + 634 = 865

Number of enalapril patients who stopped blinded medication by end of study: 1285 – 865 = 420

Final mean daily dose of enalapril:

$$\frac{(23 \times 2.5mg/d) + (86 \times 5mg/d) + (122 \times 10mg/d) + (634 \times 20mg/d) + (420 \times 0mg/d)}{(23 + 86 + 122 + 634 + 420)}$$

$$= \frac{14379.2}{1285} = 11.2\ mg/d$$

Mean enalapril daily dose among patients taking study medication:

$$\frac{(23 \times 2.5mg/d) + (86 \times 5mg/d) + (122 \times 10mg/d) + (634 \times 20mg/d)}{(23 + 86 + 122 + 634)} = \frac{14379.2}{865}$$

$$= 16.6\ mg/d$$

This suggests that the actual method applied in SOLVD-T publication could be either as proposed by the applicant or as illustrated above, without excluding patients who died before final study visit. The same calculation methodologies can be used for PARADIGM-HF and the results are summarized in Table 2.

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