

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

SUMMARY REVIEW



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Cross Discipline Team Leader Review & Divisional Memo

NDA: 206302 Nebivolol/valsartan (BYVALSON) for hypertension
Sponsor: Forest Laboratories
Review date: 24 May 2016

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This memo serves as the Cross Discipline Team Leader Review and also conveys the Division's decision to approve NDA 206302 (neбиволol/valsartan; BYVALSON) for the treatment of hypertension. This combination product was extensively reviewed by the Agency during a prior review cycle. At the end of that review cycle, the Agency issued a Complete Response Letter (NDA 206302; 24 December 2014). The current application, submitted on 29 September 2015, constitutes a complete response to the Agency's Complete Response Letter.

The applicant's resubmission has been the subject of reviews of product quality (Kambhampati; 03 May 2016), clinical pharmacology (Sahre; 29 March 2016), clinical and statistical (Xiao and Kordzakhia; 05 April 2016). All disciplines recommend approval of BYVALSON, 5 mg/ 80 mg (neбиволol/valsartan) once daily for the treatment of hypertension. Based on the stability data, a 24-month expiration period is granted for the drug product when stored in the commercial container closure under the recommended storage conditions. Labeling has also been reviewed by the Division of Medication Error Prevention and Analysis (Thomas; 23 March 2016), Office of Prescription Drug Promotion (Patel; 23 March 2016), Division of Medical Policy Programs (Booker; 23 March 2016), and Division of Pediatric and Maternal Health (Dinatale; 14 March 2016). There are no outstanding labeling issues.

The current action represents a new paradigm for approving fixed dose combinations of agents for the treatment of hypertension. This new approach is based on the principle that one might expect a more nearly additive antihypertensive effect when monotherapies with reasonably independent mechanism of action are combined at low doses. From a safety perspective, this approach would be expected to mitigate dose-related adverse effects. This concept was discussed at a Cardiovascular and Renal Drugs Advisory Committee Meeting (CRDAC) on 10 September 2014, a meeting that focused on the potential clinical utility of a fixed dose combination prescription product (composed of an antihypertensive drug, aspirin, and a statin) to reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with a history of cardiovascular disease.¹ During the meeting, Professor Nicholas Wald presented information supporting the utility of combining two blood pressure lowering

¹ Transcript for the September 10, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee. (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM435075.pdf>) Accessed on 04/28/2016.

drugs at half the standard dose compared to double the dose of monotherapy (i.e., standard or double standard). A meta-analysis of 354 randomized trials showed that at half the standard dose, antihypertensives typically produce a 20% lower effect than the standard dose indicating a classic Emax relationship. This relationship was consistent across different pharmacologic classes (thiazides, beta blockers, ACE inhibitors and calcium channel blockers).² Near additive effects were observed with half standard doses used in combination. Moreover, adverse effects attributable to the treatment, specifically for thiazides, beta-blockers and calcium channel blockers, were dose dependent. As such, there is little to be gained in blood pressure reduction with the conventional paradigm of sequentially increasing the dose of monotherapy compared to treatment with a low dose combination. Moreover, there may be a safety advantage to this approach when important risks are dose dependent, as opposed to dose independent or overlapping. The benefits of initial therapy with a lower dose ACE inhibitor/diuretic or ARB/diuretic followed by addition of other pharmacologic agents compared to conventional paradigm of starting with monotherapy was also demonstrated by Feldman et al³. These findings and the discussions at the CRDAC formed the basis for the potential path forward described in the CRL issued on 24 December 2014.

The current submission does not contain new clinical data; rather the resubmission provides re-analyses of data from the applicant's registration trial, Study NAC-MD-01, an 8-week randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study of nebivolol and valsartan given either as a fixed dose combination (FDC) or as monotherapy in patients with Stage 1 or Stage 2 hypertension. The reviews by Sahre and Xiao and Kordzakhia contain a number of analyses that support the use of a FDC of nebivolol and valsartan at a dose of 5 mg/ 80 mg (nebivolol/valsartan) for the treatment of hypertension. Below we highlight key findings that support the approval of BYVALSON 5 mg/ 80 mg (nebivolol/valsartan) for the treatment of hypertension:

- Although there is some overlap in mechanism of action (i.e. both valsartan and nebivolol reduce renin-angiotensin-aldosterone activity), nebivolol is also reported to increase both stimulated and basal endothelial nitric oxide release, an effect that is thought to contribute to its antihypertensive activity.^{4, 5, 6} Hence, there appears to be a mechanistic basis for the combination, albeit not as strong as for some other combinations of antihypertensive agents with more independent mechanisms of action.
- Consistent with the paradigm noted above, dose-response data for nebivolol and valsartan as monotherapies indicate that greater than 50% of the blood pressure

² Law MR, Wald NJ, Morris JK and Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; 326:1427 (doi: <http://dx.doi.org/10.1136/bmj.326.7404.1427>). Accessed on 04/28/2016.

³ Feldman et al. A simplified approach to the treatment of uncomplicated hypertension: A cluster randomized, control trial. *Hypertension* 2009; 53: 646 – 653 (DOI: 10.1161/HYPERTENSIONAHA.108.123455). Accessed on 04/28/2016.

⁴ According to the nebivolol label, the mechanism of action behind the antihypertensive of nebivolol has not been definitively established. The label further notes that the following factors may contribute: (1) decreased heart rate, (2) decreased myocardial contractility, (3) decreased sympathetic activity, (4) suppression of renin activity, and (5) vasodilation and decreased peripheral vascular resistance.

⁵ Tzemos N, Lim PO, and MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: A randomized, double-blind, crossover study. *Circulation*. 2001;104:511-514. Accessed on 05/21/2016.

⁶ Perros et al. Nebivolol for improving endothelial dysfunction, pulmonary vascular modeling, and right heart function in pulmonary hypertension. *JACC* 2015; 65(7):681-683. (doi:10.1016/j.jacc.2014.11.049). Accessed on 05/21/2016

lowering effect of the monotherapies is achieved with neбиволол 5 mg and валсартан 80 mg, respectively. From a safety perspective, these lower doses would also likely mitigate the risk of dose-related adverse effects.

- In Study NAC-MD-01, FDC 5 mg/80 mg produced statistically and clinically significantly greater reductions in DBP/SBP at week 4 compared to its mono-components (Least Square Mean (LSM) difference of 2.7/3.6 mmHg for FDC 5/80 mg vs neбиволол 5 mg and LSM difference of 3.3/2.9 mmHg for FDC 5/80 mg vs валсартан 80 mg). The observed contribution of валсартан 80 mg to the effect of FDC 5 mg/80 mg was 54% for DBP and 65% for SBP, while the observed contribution of neбиволол 5 mg to the effect of FDC 5 mg/80 mg was 62% for DBP and 57% for SBP. This provides evidence that each of the components make a contribution to the claimed effect at these doses.
- Near additive effects were observed with FDC 5 mg/80 mg for both DBP and SBP, with additivity ratios and differences falling within the range of recently approved FDCs. The additivity ratio (the BP reduction observed with the FDC divided by the sum of the BP reductions of the FDC's components) was 0.87 and 0.82 for DBP and SBP, respectively. The additivity difference (the subtractive difference between the BP reduction from the FDC and the sum of the BP reductions of the FDC's components) was -1.1 mm Hg and -1.8 mm Hg for DBP and SBP respectively.⁷
- Dose-response data for the FDC over the range of 5 mg/80 mg to 20 mg/320 mg indicate that the relationship is shallow over this range. A comparison of FDC 5 mg/80 mg (week 4) and FDC 20 mg/320 mg (week 8) shows a difference of 20%, further indicating that majority of the effect are attained by the low dose combination (5 mg/80 mg) and that there is little to be gained with increasing the dose of the FDC.
- From a safety and tolerability perspective, FDC 5 mg/80 mg is well tolerated.
- As discussed in the primary reviews, a major focus of discussion has been the dose of neбиволол/валсартан that should be approved. The applicant initially proposed approval of the (b) (4) dose as opposed to the 5/80 mg dose. (b) (4)
Given these data as well as the data noted above, a dose of 5/80 mg is the sole dose that will be approved.

⁷ As noted in the Clinical and Statistical Review, values less than one for the additivity ratio correspond to partial additivity whereas values equal to one and greater than one correspond to complete additivity and super-additivity or synergy, respectively. Negative values for the additivity difference indicate partial additivity, a value of 0 indicates complete additivity, and positive values indicate synergy.

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