CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22511Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-511 / 00
Drug Name:	Vimovo® (naproxen/esomeprazole magnesium) Tablets
Indication(s):	Signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID associated gastric ulcers
Applicant:	AstraZeneca
Date(s):	Letter date: 6/30/09
	PDUFA date: 4/30/10
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
Statistical Reviewer for DGP:	Freda Cooner, Ph.D. (DB3)
Medical Division:	Division of Anesthesia and Analgesia Products (DAAP)
	Consult from Division of Gastroenterology Products (DGP)
Clinical Team:	Medical Officer: Jin Chen, M.D. (DAAP)
	Medical Team Leader: Ellen Fields, M.D. (DAAP)
Project Manager:	Anne Simon (DGP)

Keywords: Clinical studies; NDA review; Non-inferiority Comparisons

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The applicant submitted results from four Phase 3 clinical studies intended to assess the efficacy of Vimovo (naproxen/esomeprazole magnesium) Tablets. The applicant is seeking an indication for treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers.

This review will only cover two of the clinical studies (307 and 309) which were conducted in patients with osteoarthritis (OA) of the knee and assessed the efficacy of VIMOVO for treatment of the signs and symptoms of OA. Both studies included three double-blind treatment arms: Vimovo 500 mg/20 mg twice daily, Celecoxib 200 mg once daily, and placebo.

The applicant has requested the following language in the Clinical Studies section of the label (Section 14) which constitutes a comparative claim: (b) (4)

The results of the two studies were conflicting, (b) (4). In both studies, the results indicate that VIMOVO was not non-inferior to the celecoxib arm, but was statistically significantly superior to placebo. Based on the comparisons to placebo in the two studies, there is sufficient evidence to support the efficacy of VIMOVO for the indication of treatment of OA signs and symptoms. (b) (4)

1.2 Brief Overview of Clinical Studies

The naproxen component is currently approved for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Two of the clinical studies submitted assessed the efficacy of the combination product for this indication. Those studies (307 and 309) will be discussed in this review.

The esomeprazole magnesium component is currently approved for treatment of gastroesophageal reflux disease and risk reduction of NSAID-associated gastric ulcer. Two clinical studies (301 and 302) assessed the efficacy of the combination product for the latter indication. Those studies will be reviewed by Dr. Freda Cooner (Division of Biometrics 3) for the Division of Gastroenterology Products (DGP).

The applicant conducted two prospectively planned, randomized, double-blind, active- and placebo-controlled clinical studies to assess the efficacy of Vimovo for the treatment of signs and symptoms of osteoarthritis (OA). Both studies (307 and 309) had the same design, treatment groups, patient population, efficacy endpoints, planned sample size, and planned analyses.

Patients were adults, ages 50 and older, with a history of at least 6 months of osteoarthritis of the knee. They had to be on a stable dose of NSAIDs, COX-2 inhibitors, or other oral analgesic therapy for at least 6 weeks prior to screening. When the oral analgesic therapy was discontinued, patients who experienced an OA flare, defined as worsening of pain and patient global assessment, were eligible for randomization.

The three double-blind treatment arms were VIMOVO 500 mg/20 mg twice daily (bid), celecoxib 200 mg once daily (qd), and placebo. In each study, eligible patients were randomized using a ratio of 2:2:1 to the three treatment groups.

In both protocols, the applicant stated the primary objective was to demonstrate that VIMOVO was non-inferior to celecoxib 200 mg qd on three primary endpoints: WOMAC pain subscale, WOMAC function subscale, and Patient Global Assessment. All three endpoints are measured on 0-100 mm VAS scales. The applicant planned to show efficacy on all three endpoints and did not plan any statistical adjustment for multiplicity. These have historically been the three efficacy endpoints required by the Agency for the indication of the treatment of signs and symptoms of OA.

Patients were treated for 12 weeks. The timepoint of interest was the change from baseline to Week 12 for the three efficacy measures. These studies did not assess the incidence of gastric ulcers.

The planned primary analysis used an ANCOVA model with terms for treatment and baseline pain as the covariate. The applicant's stated hypothesis was non-inferiority of the VIMOVO treatment group to the celecoxib treatment group on all three endpoints. Non-inferiority was assessed using 95% confidence intervals on the difference between the VIMOVO and celecoxib groups.

The applicant stated in the protocols that a non-inferiority margin of 10mm on the 0-100 mm VAS scales would be used for the comparisons. This was not agreed to by the Agency prior to conducting the studies. Discussion with the Agency on June 10, 2008, described the factors of the analysis which would impact the NI conclusions, including the treatment effect sizes and consistency of treatment response.

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