**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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| NDA | **22511** |
| Submission Date (s) | **06-07-2016, 11-09-2016, 1-6-2017, 1-11-2017, 1-23-2017, 2-6-2017, 2-24-2017, 3-31-2017, 4-26-2017**<br>**Study Report : 12-15-2015** |
| PDUFA Date: | **07-06-2017** |
| Brand Name | **Vimovo** |
| Generic Name | **Naproxen / Esomeprazole Magnesium** |
| Submission Type | **Efficacy Supplement** |
| Dosage Form, Strength | **375 mg Naproxen DR /20 mg Esomeprazole IR**<br>**500 mg Naproxen DR /20 mg Esomeprazole IR** |
| Indication | **For relief of signs and symptoms of rheumatoid arthritis (RA) in patients at risk of developing NSAID-associated gastric ulcers** |
| Applicant | **Horizon Pharma Inc.** |
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# 1. Executive Summary

This pediatric efficacy supplement is in response to PMR 1634-2 which was issued with the approval letter for Vimovo in 2010.

Vimovo is a fixed dose combination product containing naproxen and esomeprazole, which was approved in April 30, 2010 for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in adult patients at risk of developing NSAID associated gastric ulcers. Approved Vimovo dose/dosing regimen is one tablet twice daily of 375 mg naproxen/20 mg esomeprazole or 500 mg naproxen/20 mg esomeprazole. Vimovo tablet is formulated as an enteric-coated naproxen core and an immediate-release esomeprazole magnesium layer surrounding the core.

For relief of signs and symptoms of rheumatoid arthritis (RA) in patients at risk of developing NSAID-associated gastric ulcers, the Agency considered the extrapolation of efficacy for Vimovo from adults to pediatric patients as a reasonable option since both the juvenile and adult arthritis are treated with NSAIDs and this common use of NSAIDs puts both pediatric and adult patients at risk of developing NSAID-associated gastric ulcers[1].

The following PMR was issued to collect additional information, particularly dosing and safety data for the combination product in pediatric adolescent patients to support this indication:

> PMR 1634-2: Deferred pediatric study under PREA in children 12 years to 16 years and 11 months of age with Juvenile Rheumatoid Arthritis (JRA).
>
> A safety and population pharmacokinetic (PK) study in adolescents with JRA who are ages 12 years to 16 ears and 11 months and require treatment with NSAIDs will be conducted. This study will be a 6 month, multicenter, open-label study to evaluate the safety and PK of VIMOVO in this age group.

There are no products that are approved for the relief of signs and symptoms of rheumatoid arthritis (RA) in patients at risk of developing NSAID-associated gastric ulcers in adolescents.

On the other hand, there is prior data with both active ingredients of Vimovo individually in pediatric patients. Naproxen is approved for juvenile arthritis (JA) in pediatric patients ≥2 years of age. Although esomeprazole (Nexium) currently does not have the indication for risk reduction of NSAID-associated gastric ulcer in adolescent patients, it is approved for healing of erosive esophagitis and symptomatic gastroesophageal reflux disease (GERD) in 1-17 years of age patients. The approved doses of Nexium in adolescences are same as for adults.

In fulfillment of PMR 1634-2, the applicant had conducted study D1120C00037 entitled "A 6-month, Multicenter, Open-label, Safety Study of VIMOVO (250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg Naproxen/Esomeprazole) in Adolescents Aged 12 to 16, Inclusive, with Juvenile Idiopathic Arthritis (JIA)".

[1] Refer to PMHS review for NDA 22511 dated 02/16/2010

This review discusses the appropriateness of the studied doses in this trial and dosing recommendation for adolescent patients with JIA. Please refer to the clinical review by Dr. Majorie Dannis dated 03/01/2017 for the safety assessment of Vimovo in adolescent patients.

At the time of initial submission of the study results, the applicant proposed the update in the label only to sections 8.4 (pediatric use) and 12.3 (pharmacokinetics) and corresponding sections of highlights in the label but did not seek an indication nor propose specific dosage regimen for the adolescent patients.

However, based on the comparable plasma exposures of both naproxen and esomeprazole components of Vimovo between the adults and adolescent at the studied doses in this submission and the prior knowledge for both components in adolescent patients, we have concluded that it is reasonable to extrapolate the efficacy of Vimovo from adults to adolescent with JIA at the studied doses (Table -1).

We, however, recommend that the use of Vimovo be limited to adolescent patients who weight 38 kg or greater because of the following reasons: 1) the sponsor did not propose marketing of the 250 mg naproxen/20 mg esomeprazole of Vimovo strength studied in adolescent patients < 38 kg and 2) this strength is not an approved marketed strength in adults currently. In addition, we recommend both 375 mg/20 mg and 500 mg/20 mg for patients > 75 kg to allow dosing flexibility although only 500 mg/20 mg was studied in patients >75 kg. It is because both 375 mg/20 mg and 500 mg/20 mg are approved for adult patients regardless of body weight and use of the lowest effective dose between 375 mg or 500 mg naproxen is recommended. This dosing recommendation in adolescent JIA patients >75 kg will be consistent with approved Vimovo doses for adult patients.

*Table -1: Vimovo doses Studied in Study 037 and OCP recommended Vimovo Doses in JIA pediatric patients 12 years of age and older*

| Body Weight | Vimovo Doses Studied in Study 037 | OCP Recommended Vimovo Dose |
|---|---|---|
| **<38 kg** | 250 mg/20 mg tablets BID | None |
| **38 kg to <50 kg** | either 250 mg/20 mg<br>or 375 mg/20 mg tablets BID | 375 mg/20 mg tablets BID |
| **50 kg to <75 kg** | either 375 mg/20 mg<br>or 500 mg/20 mg tablets BID | either 375 mg/20 mg<br>or 500 mg/20 mg tablets BID |
| **≥75 kg** | 500 mg/20 mg BID | either 375 mg/20 mg<br>or 500 mg/20 mg tablets BID |

## 1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached between the FDA and the applicant. From a clinical pharmacology standpoint, the sponsor fulfilled the PREA PMR1634-2.

Clinical Pharmacology recommends the following dosage regimen to be added to section 2 DOSAGE AND ADMINISTRATION:

Juvenile Idiopathic Arthritis in Pediatric Patients 12 Years of Age and Older and Weighing at Least 38 kg:

- Body weight of 38 kg to <50 kg: Vimovo 375 mg/20 mg tablets twice daily

- Body weight of > 50 kg: either Vimovo 375 mg/20 mg or 500 mg/20 mg tablets twice daily

Refer to the final label for detailed labeling languages in Section 2, 8.4 and 12.3.

## 1.2 Summary of Important Clinical Pharmacology Findings

Appropriateness of the studied doses for pediatric patients with JIA
We have found that the doses studied in the PK and safety trial in adolescent patients with JIA (study 037) are appropriate and in support of the extrapolation of the efficacy of Vimovo from adults to adolescents with JIA based on the comparable plasma exposures to both naproxen and esomeprazole components of Vimovo between the adults and adolescents and the prior knowledge for both components in adolescent patients. We recommend the following dosing regimens for JIA in pediatric patients 12 years of age and older:

- Body weight of 38 kg to <50 kg: 375 mg/20 mg tablet twice daily
- Body weight of > 50 kg: either 375 mg/20 mg or 500 mg/20 mg tablet twice daily

This dose recommendation is in line with studied doses in study D1120C00037 and Applicant's proposal in a response to FDA information request (IR) dated March 24, 2017.

Comparison of the systemic exposure to naproxen component of Vimovo between adolescents and adults:
The dosage regimens of Vimovo evaluated in the submitted adolescent study were weight based for naproxen component as following:

- Baseline weight < 38 kg: 250 mg/20 mg tablet BID
- Baseline weight of 38 kg to < 50 kg: either 250 mg/20 mg or 375 mg/20 mg tablet BID
- Baseline weight of 50 kg to < 75 kg: either 375 mg/20 mg or 500 mg/20 mg tablet BID
- Baseline weight ≥75 kg: 500 mg/20 mg BID

At steady state, the naproxen concentrations from Vimovo observed in the adolescent patients (n=46) in Study 037 were comparable to those observed in healthy adults who received 500 mg naproxen VIMOVO regardless of naproxen doses in adolescent (250 mg, 375 mg and 500 mg depending on body weight band). Of note, the insufficient PK blood sampling limited the adequate analyses of PK parameters. According to the Naprosyn label, 5 mg/kg single dose naproxen suspension (recommended dose for pediatric JRA > 2 years old) in pediatric patients produced similar plasma exposure to those seen in adults taking 500 mg, which also supports the extrapolation of efficacy at the studied doses for naproxen component of Vimovo from adults to adolescence with JIA.

However, since the 250 mg naproxen/20 mg esomeprazole of Vimovo is currently not an approved marketed strength in adults and the sponsor did not seek marketing of this new strength in this submission, we recommend that the use of Vimovo be limited to patients who weight 38 kg or greater. In addition, since the recommended Vimovo dose in adult patients is to use the lowest effect dose of 375 mg or 500 mg naproxen without any specification of body weight, restricting adolescent patients who weighs 75 kg or greater to only 500 mg naproxen/20 mg esomeprazole of Vimovo does not appear to be necessary.

Comparison of the systemic exposure to Esomeprazole Component of Vimovo between adolescents and adults:

At steady state, plasma concentrations of esomeprazole from Vimovo observed in the adolescent JIA patients were in similar range as to the plasma concentrations of esomeprazole from Vimovo in healthy adults. It was noted that most of the observed esomeprazole concentrations in JIA adolescent patients were in lower end of the concentrations that were observed in healthy adults. This could be due to limited PK sampling around $C_{max}$ in combination with a high variability of PK of esomeprazole in JIA pediatric patients.

Consistent with the observed plasma concentrations, although the estimated individual esomeprazole CL/F and AUC values in adolescents through population PK analysis were generally within the range that was observed in adults, the estimated geometric means of CL/F and V/F in adolescent were higher, and thus the estimated geometric mean values of AUC in adolescent were lower than those in adults. Nonetheless, the reliability of these estimated PK parameters in adolescent patients via population PK analysis are questionable due to its limited PK sampling only to early time points in JIA adolescent patients, which could lead to higher estimates of CL/F and consequently lower estimates of AUC in JIA patients compared to those in the adult studies which had multiple measurements at later time points up to 24 hours post-dose.

Based on prior knowledge, PK of omeprazole from delayed release omeprazole formulation (Nexium) in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. The difference in formulation (IR in Vimovo vs. DR in Nexium) may affect the absorption phase of the esomeprazole PK. However, the clearance of esomeprazole is not anticipated to be impacted by the formulation difference.

Current observations of comparable plasma concentrations despite their limitation, and prior knowledge about esomeprazole PK in adolescents support the same dose for esomeprazole component for adolescents and adults and the extrapolation of efficacy at the studied dose for reducing the risk for developing NSAID associated gastric ulcers from adults to adolescents.

# 2 Question-Based Review

## 2.1 General Attributes of the drug

### 2.1.1 What are the highlights of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology review?

Vimovo® is an oral fixed dose combination tablet product containing 375 mg or 500 mg naproxen (a nonsteroidal anti-inflammatory drug) in the enteric coated (EC) core surrounded by 20 mg esomeprazole (PPI, present as 22.3 mg esomeprazole magnesium trihydrate) in the immediate-release (IR) film coat.

### 2.1.2 What is the regulatory background?

Vimovo was approved in April 30, 2010 for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. Vimovo tablets are to be taken orally twice daily.

The original NDA application for Vimovo was approved via a 505b(2) pathway with two reference-listed products shown below.

| Reference listed Drug | NDA # | Sponsor | Strength | Formulation | Approved Year |
|---|---|---|---|---|---|
| EC Naprosyn | 020067 | Roche | 375 mg & 500 mg | EC | 1994 |
| Nexium capsules | 021153 | AstraZeneca | 20 mg | EC | 2001 |

EC-Naprosyn is approved for the indications of Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis at both 375 mg and 500 mg doses for twice daily administration.

Nexium, delayed release esomeprazole, is approved for risk reduction of NSAID-associated gastric ulcer 20 mg or 40 mg once daily for up to 6 months.

The clinical efficacy of Vimovo in treating osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis was established in part through the demonstration of bioequivalence of naproxen component in Vimovo to enteric-coated naproxen, EC- Naprosyn® at both 375 mg and 500 mg strength. Two phase 3 trials (active and placebo controlled) were conducted to evaluate the efficacy of the naproxen component of Vimovo for treatment of signs and symptoms of osteoarthritis.

Efficacy and safety for Vimovo for reduction of gastric ulcer was established in two phase 3 studies of 6 months duration in which the Vimovo 500 mg naproxen dosage form (500 mg naproxen/immediate release esomeprazole 20 mg) was compared to EC-Naprosyn 500 mg, both administered twice daily.

In a relative BA study, 20 mg IR esomeprazole from Vimovo has approximately 50% lower AUC compared to EC esomeprazole from Nexium following a single dose administration. The relative BA at steady state was not assessed.

The following PMR was issued in the approval letter:

> PMR 1634-2: Deferred pediatric study under PREA in children 12 years to 16 years and 11 months of age with Juvenile Rheumatoid Arthritis (JRA).
>
> A safety and population pharmacokinetic (PK) study in adolescents with JRA who are ages 12 years to 16 ears and 11 months and require treatment with NSAIDs will be conducted. This study will be a 6 month, multicenter, open-label study to evaluate the safety and PK of VIMOVO in this age group.

Initially, the applicant did not seek any additional indication in adolescent patients, and thus, did not propose any specific dosing recommendation in the adolescent patient at the time of the submission. The proposed edits to the label were only for changes to sections 8.4 (pediatric use) and 12.3 (pharmacokinetics) and corresponding sections of highlights.

### 2.1.3 Were naproxen and esomeprazole approved previously for pediatric use in adolescents?

Yes. Both naproxen and esomeprazole have been approved previously in adolescent population.

Naproxen is approved for juvenile arthritis (JA) pediatric patients ≥2 years of age since 1987, and naproxen suspension (Naprosyn Suspension) is approved for juvenile rheumatoid arthritis patients in order to obtain the maximum dosage flexibility based on the patient's weight. The approved total daily dose of naproxen for JA is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day) with total daily dose not exceeding 15 mg/kg/day. 5 mg/kg single dose naproxen suspension in pediatric patients produced similar plasma exposure to those seen in adults taking 500 mg. The terminal half-life of naproxen appears to be similar in pediatric and adult patients. EC-NAPROSYN has not been studied in subjects under the age of 18.

Esomeprazole (Nexium) currently does not have the indication for risk reduction of NSAID-associated gastric ulcer in adolescent patients. However, esomeprazole PK does not appear to be impacted by disease status since esomeprazole PK parameters are similar between the healthy subjects and patients with symptomatic gastroesophageal reflux disease (GERD) (table 2).

*Table 2: The Mean Pharmacokinetic Parameters of NEXIUM 40 mg on Day 5 Following Oral Dosing for 5 Days*

| Parameters | Healthy adult subjects | Adult GERD Patients |
|---|---|---|
| AUC (μmol·h/L) | 11.21 | 12.6 |
| $C_{max}$ (μmol/L) | 4.64 | 4.7 |
| $t_{1/2}$ (h) | 1.25 | 1.5 |

Source: Clinical Pharmacology Review for Nexium, NDA 21153 and Source: Nexium Prescription label

However, Nexium (delayed release esomeprazole) is approved for healing of erosive esophagitis and symptomatic gastroesophageal reflux disease (GERD) in 1-17 years of age patients. The approved doses in adolescences are same as for adults (table-3):

*Table 3: Recommended Dosage Schedule for Nexium*

| Age Group | Indications | Dose | Frequency |
|---|---|---|---|
| Adults | Healing of Erosive Esophagitis | 20 mg or 40 mg | Once daily for up to 4 to 8 weeks |
| | Symptomatic GERD | 20 mg | Once daily for up to 4 (b) (4) |
| Adolescent 12-17 years | Healing of Erosive Esophagitis | 20 mg or 40 mg | Once daily for up to 4 to 8 weeks |
| | Symptomatic GERD | 20 mg | Once daily for up to 4 |

Source: Nexium Prescription label

Nexium PK in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In this submission, the applicant conducted one study D1120C00037 entitled "A 6-month, Multicenter, Open-label, Safety Study of VIMOVO (250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg Naproxen/Esomeprazole) in Adolescents Aged 12 to 16, Inclusive, with Juvenile Idiopathic Arthritis (JIA)". (This study will also be referred as Study 037 throughout the review). The study was Phase 4, US only, multicenter, open-label, single arm, non-comparator study designed to evaluate the safety of VIMOVO (250 mg/20 mg, 375 mg/20 mg, or 500 mg/20 mg naproxen/esomeprazole) in the treatment of JIA in adolescent patients for up to 6 months to fulfill a FDA Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) 1634-2.

A total of 46 patients aged 12 to 16 years diagnosed with JIA were enrolled into the study. Thirty-six patients completed 6 months of study drug treatment, and 10 patients discontinued prematurely (4 because of AEs, 1 because of severe protocol noncompliance, 2 were lost to follow-up, and 3 withdrew consent).

The VIMOVO dose for each patient was determined by the patient's weight at baseline and the Investigator's discretion according to published clinical guidelines for naproxen use (Cassidy 2011). The target dose of the naproxen component was within the range of 10-20 mg/kg/day divided twice daily (BID) with a maximum daily dose of 1000 mg.

- Baseline weight <38 kg: 250 mg/20 mg tablets BID
- Baseline weight of 38 kg to <50 kg: either 250 mg/20 mg or 375 mg/20 mg tablets BID
- Baseline weight of 50 kg to <75 kg: either 375 mg/20 mg or 500 mg/20 mg tablets BID
- Baseline weight ≥75 kg: 500 mg/20 mg BID

The tablets were taken whole, orally, and swallowed whole with liquid on an empty stomach at least 30 minutes before the morning and evening meals.

Out of 46 subjects, 4 patients were assigned to the 250 mg/20 mg dose group, 20 subjects were assigned to the 375 mg/20 mg dose group and 22 subjects were assigned to the 500 mg/20 mg dose group based on their baseline weights.

The PK samples were collected when the exposure to naproxen and esomeprazole were at steady state. Frequent PK samples were collected on Month 1(day 23-37) in up to 8 patients at prior to morning dose intake and at 0.5, 1, 1.5, and 3 hours (±5 minutes) following morning dose intake. Sparse PK samples were collected on Months 1 (Day 23-37) and 3 (Day 83-97) by collecting a single PK sample from remaining patients who did not participate in frequent sampling. The sample was obtained 0.5 to 1 hour following intake of the morning dose at 1 of these visits and between 2 to 3 hours following intake of the morning dose at the other visit.

### 2.2.2 Is the PK for naproxen component of Vimovo similar between adults and adolescents?

*At steady state with limited PK samples, the naproxen concentrations from Vimovo observed in the adolescent patients (n=46) in the study 037 after weight based dosing, regardless of naproxen dose in adolescent (250 mg, 375 mg and 500 mg), were comparable to those observed in healthy adults who received 500 mg naproxen VIMOVO. (PK data were only collected up to 3 hours post-dose during the absorption phase in adolescent patients). This similarity in naproxen plasma concentrations, although with very limited PK data, supports the extrapolation of naproxen efficacy from Vimovo from adults to adolescent as EC-naproxen is already approved for juvenile arthritis (JA) in pediatric patients ≥2 years of age. According to the EC-Naprosyn label, 5 mg/kg single dose naproxen suspension (recommended dose for pediatric JRA) in pediatric patients produced similar plasma exposure to those seen in adults taking 500 mg, which also supports the extrapolation of efficacy for naproxen component of Vimovo from adults to adolescence with JIA.*

*Note that the applicant did not have adequate data to compare the $C_{max}$ of naproxen from Vimovo in pediatric adolescent population in this study to that of adults. Population PK analysis for naproxen was not feasible due to PK sampling limitation.*

Comparison of Naproxen Systemic Exposure:

The observed plasma concentrations of naproxen from Vimovo in adolescent JIA patients in study 037 were compared with plasma concentrations of naproxen at different doses from Vimovo in healthy adults (Study PN400-104, PN400-105 and D1120C0040) and with pediatric naproxen PK profiles from naproxen suspension in a published literature (Table-4)[2]. The study results of PN400-104 (500 mg naproxen dose) and PN400-105 (375 mg naproxen dose) in healthy adults were submitted and reviewed by the FDA during the initial submission of Vimovo dated 6/30/2009. Please see the Clinical Pharmacology review for NDA 22511 dated 4/8/2010 for detailed review of these two studies. Of note, the comparison of naproxen concentrations in adolescent patients with that after 250 mg naproxen/20 mg esomeprazole in healthy adults or with published data for naproxen suspension should be considered only exploratory as full study reports for study D1120C0040 with 250 mg naproxen/20 mg esomeprazole in healthy adults and pediatric naproxen PK profiles from naproxen suspension in literature were not submitted for our review.

*Table-4: Study Design Comparison between Pediatric JIA Study and Healthy Adult studies*

| Description | Pediatric study (D1120C00037) | Healthy Adults (PN400-104) | Healthy Adults (PN400-105) | Healthy Adult (D1120C0040) | Pediatric study Naproxen suspension (Ansell et al. 1975) | Pediatric study Naproxen suspension (Valitalo et al.2012) |
|---|---|---|---|---|---|---|
| Number of patients | n = 41 | n = 28 | n = 30 | N= 28 | n = 9 | n = 53 |
| Age range | 12-17 years | 18-34 years | 19-54 years | 18-53 years | 5-14 years | 0.25-12 years |
| Dosage | 250 mg/20 mg, 375 mg/20 mg, 500 mg/20 mg naproxen/ esomeprazole depending upon body weight | 500 mg/20 mg naproxen/ esomeprazole | 375 mg/20 mg naproxen/ esomeprazole | 250 mg/20 mg naproxen/ esomeprazole | 5 mg/kg naproxen suspension; dose range 122.5 – 250 mg | 10 mg/kg naproxen suspension; |
| Dosing frequency | Multiple doses | Multiple doses | Single dose | Single dose | Single dose | Single dose |
| Time of PK sampling | Month 1 & 3 | Day 9 | Day 1 | Day 1 | Day 1 | Day 1 |
| Food intake | Not specified | Fasted | Fasted | Fasted | Not specified | Not specified |
| Sampling frequency | Mostly sparse (1-2 PK samples); 6 subjects contributing 3-4 PK samples | Rich sampling (28 PK samples per patient) | Rich sampling (20 PK samples per patient) | Rich sampling (20 PK samples per subject) | Post-dose 1, 2, 12 and 24 hours | 2-7 samples/patients between 13 minutes and 51 hours post-dose |
| Lower limit of quantification | 0.1 µg/mL | 0.1 µg/mL | 0.1 µg/mL | 25 nmol/L (8.635 ng/mL) | Not specified | Not specified |

A. $C_{max}$ Comparison:

[2] Please note that Study PN400-101(500 mg naproxen dose/20 mg esomeprazole) from initial submission for Vimovo that was used for esomeprazole plasma concentration comparison in this review in section 2.2.3 also had single dose and multiple dose PK data for naproxen component. However, the applicant did not utilize this data for concentration comparison purpose for naproxen component.

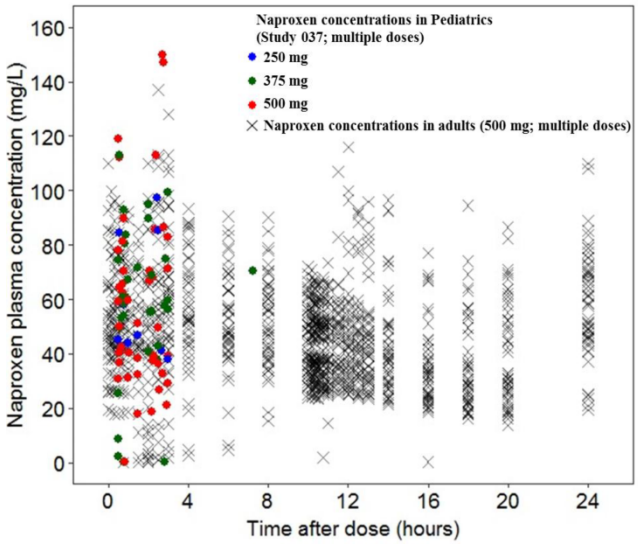
The applicant did not conduct population PK analysis for naproxen component due to sparse nature of the PK sampling data. Only $C_{max}$ values were estimated and compared between the pediatric population and adults. However, the estimated $C_{max}$ for the pediatric population in this study may not be reliable due to limited PK sampling (PK sampling only up to 3 hours post-dose where $t_{max}$ is typically around 4 hours). In addition, of the 41 patients, only 4 patients had more than two PK samples that allowed the approximation of $C_{max}$ resulting in unreliable $C_{max}$ comparison between adolescent and adults. Please see Appendix for more detail.

B. Plasma Concentration Comparison:

The observed plasma concentrations of naproxen from Vimovo in adolescent population in this study were compared with those of adults who took Vimovo tablets and as well as pediatric patients who took naproxen suspension (Table-3). As naproxen plasma drug concentrations accumulate upon multiple dosing, it is appropriate to compare adolescent naproxen PK data from Vimovo in the study 037 (PK samples were collected at Month 1 and 3) with the adult naproxen PK data at the steady state. However, only 500 mg naproxen/20 mg esomeprazole Vimovo dose in healthy adults had multiple dose PK data from the previous submissions.

Regardless of naproxen doses (250 mg, 375 mg and 500 mg based on body weight band), the naproxen concentrations from Vimovo observed in the pediatric study (Study 037) with weight based dosing for naproxen, were comparable to what were previously observed in healthy adults who took 500 mg naproxen VIMOVO at steady state during the absorption phase (Figure -1). According to the EC-Naprosyn label, 5 mg/kg single dose naproxen suspension (approved dose for pediatric JRA) in pediatric patients produced similar plasma exposures to those seen in adults taking 500 mg, which also supports the extrapolation of efficacy for naproxen component of Vimovo from adults to adolescence with JIA.

*Figure-1: Naproxen concentrations in adolescent patients from Study 037 compared to those in healthy adult subjects receiving multiple doses of **500** mg naproxen/20 mg esomeprazole twice daily*




Source: Sponsor's PK analyses report dated 01/20/2017 in response an IR, Figure 2; cross-study comparison

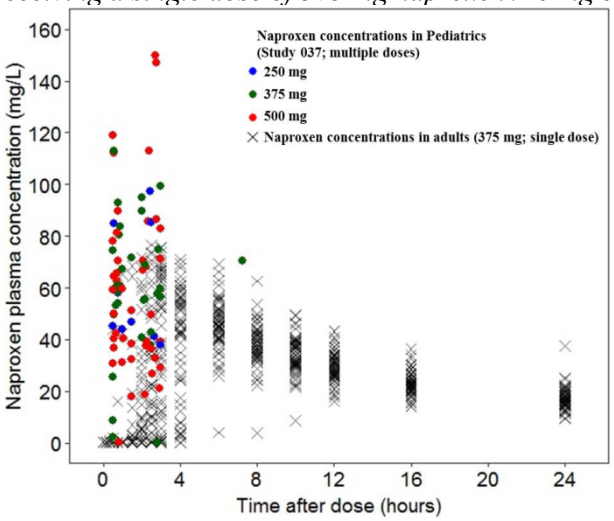
The naproxen concentrations in the pediatric study (Study 037) were higher than what were previously observed in healthy adults who took single dose of 250 mg (Figure-3) and 375 mg (Figure -2) naproxen as VIMOVO and in pediatric juvenile arthritis patients who took single dose of 5 mg/kg naproxen suspension, an approved dose for JA (Figure -4). The differences in PK

observations could be due to differences in dosing regimens (single dose vs. multiple doses) as naproxen exposure accumulation after multiple days of dosing.

There is approximately 1.70 to 2.63-fold increase in $AUC_{0-10}$, which is more relevant to this study as the PK samples were collected following the morning dose in this study.

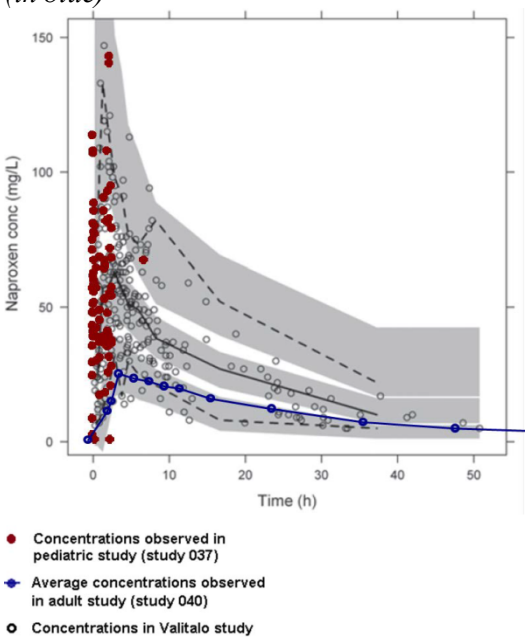
There is approximately 1.37 fold accumulation in $AUC_{0-24}$

*Figure-2: Naproxen concentrations in adolescent patients from Study 037 compared to those in healthy adult subjects receiving a single dose of **375** mg naproxen /20 mg esomeprazole*




Source: Sponsor's PK analyses report dated 01/20/2017 in response an IR, Figure 1

*Figure-3: Naproxen concentrations in adolescent patients from Study 037 ( in red) compared to those in Pediatric patients receiving a single dose of 10 mg/kg dose of naproxen suspension (in black ) and healthy adult subjects receiving single dose of 250 mg naproxen/20 mg esomeprazole (in blue)*




PK data for single dose 10 m/kg naproxen is from Valitalo P, Kumpulainen E, Manner M, Kokki M, Lehtonen M, Hooker AC, et al. Plasma and cerebrospinal fluid pharmacokinetics of naproxen in children. J Clin Pharmacol. 2012;52(10):1516-26.

*The black line on the center represents median observed concentrations and the dotted black lines 2.5th and 97.5th percentile intervals for observations. The gray areas represent 95 % confidence intervals for 2.5th, 50th and 97.5th percentile prediction intervals.*
Source: Sponsor's Study report for protocol D1120C00037, Figure 11-1

The VIMOVO naproxen concentrations observed in this pediatric study 037, regardless of naproxen dose (250 mg, 375 mg and 500 mg) are comparable to what has been previously observed in pediatric patient received a single dose of 10 mg/kg naproxen suspension (Figure -3). However, this dose is higher than the recommended dose of 5 mg/kg naproxen suspension for JA. Although this is not an approved dose, in clinical practice the doses ranging 5- 10 mg/kg BID have been used.

### 2.2.3 Is the PK for esomeprazole component of Vimovo similar between adults and adolescents?

*Yes. The totality of evidence from current observation and prior knowledge from Nexium in adolescents suggest that esomeprazole from Vimovo would have similar PK in adolescent compared to that in adult, which supports the extrapolation of efficacy of reducing the risk for developing NSAID associated gastric ulcers from adults to adolescents.*

- *Plasma concentrations of esomeprazole from Vimovo observed in the adolescent JIA patients were comparable or in similar range as to the plasma concentrations of esomeprazole from Vimovo in healthy adults following multiple dosing. Although most of the observed esomeprazole concentrations in JIA adolescent patients were in lower end of the concentrations that were observed in healthy adults, this could be due to limited PK sampling around $C_{max}$ in combination with a high variability of PK in JIA pediatric patients*
- *Consistent with the observed plasma concentrations, although the estimated individual esomeprazole CL/F and AUC values in adolescent through population PK analysis were generally within the range that were observed in adults, the estimated geometric means of CL/F and V/F in adolescent were higher, and thus the estimated geometric mean of AUC in adolescent were lower than that in adults. Nonetheless, the reliability of these estimated PK parameters in adolescent patients are questionable due to its limited PK sampling only to early time point in JIA adolescent patient, which could lead to higher estimates of CL/F and consequently lower estimates of AUC in JIA patients compared to those in the adult studies which had multiple measurements at later time points up to 24 hours post-dose.*
- *Based on prior knowledge, delayed release esomeprazole PK from Nexium in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. The difference in formulation (IR in Vimovo vs. DR in Nexium) may affect the absorption phase of the esomeprazole PK. However, the clearance of esomeprazole is not anticipated to be impacted by the formulation difference.*

#### 2.2.3.1 Comparison with Healthy Adults:

The PK profiles and parameters of esomeprazole from Vimovo in adolescent JIA patients in study 037 were compared with those from Vimovo in healthy adults following multiple dosing (Study PN400-101 & PN400-111). These studies in healthy subjects with multiple dosing were submitted and reviewed by FDA during the initial submission of Vimovo dated 6/30/2009. Please see the Clinical Pharmacology review for NDA 22511 dated 4/8/2010 for detailed review of these two studies. These two studies were chosen for the comparison to as they share similarity in study design with adolescent study 037 (i.e., PK sampling after multiple dosing and after AM doses).

*Table-5: Comparison of study design between the pediatric and adult studies*

| Description | Study 037 (n = 42) | PN400-101 (n = 19) | PN400-111 (n = 18) |
|---|---|---|---|
| Population | Adolescents with JIA | Adult healthy volunteer | Adult healthy volunteer |
| Age range | 12.0-16.9 | 43 – 65 | 22 – 52 |
| Dosage | 250 mg/20 mg, 375 mg/20 mg, 500 mg/20 mg naproxen/esomeprazole depending upon body weight | 500 mg/20 mg naproxen/esomeprazole was included in current analysis* | 500 mg/20 mg naproxen/esomeprazole was included in current analysis |
| Dosing frequency | Multiple doses; BID | Multiple doses; BID on day 1-14 (Data from day 14 were used for analysis) | Multiple doses; QD on day 1 &10; BID day 2-9 (Data from period 1, day 10 were used for analysis) |
| Food intake | Foods allowed after 30 minutes after dose | Foods allowed after 60 minutes after dose | Foods allowed after 60 minutes after dose |
| Sampling frequency | Mostly sparse (1-2 PK samples); 6 subjects contributing 3-4 PK samples | Rich sampling (28 PK samples per patient) | Rich sampling (17 PK samples per patient) |
| LLOQ for the assay | 20 nmol/L (6.908 ng/mL) | 1 ng/mL | 1 ng/mL |

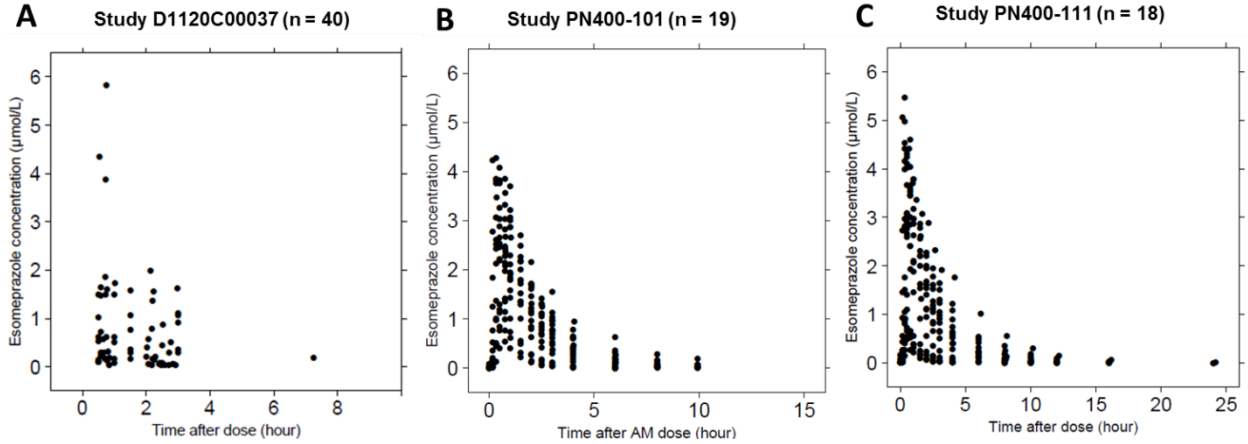
Abbreviations: LLOQ, lower limit of quantification.
* Other dose strength includes 500 mg/10 mg and 500 mg/30 mg naproxen/esomeprazole.

Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Table 3

**A:** *PK Profile Comparison:*

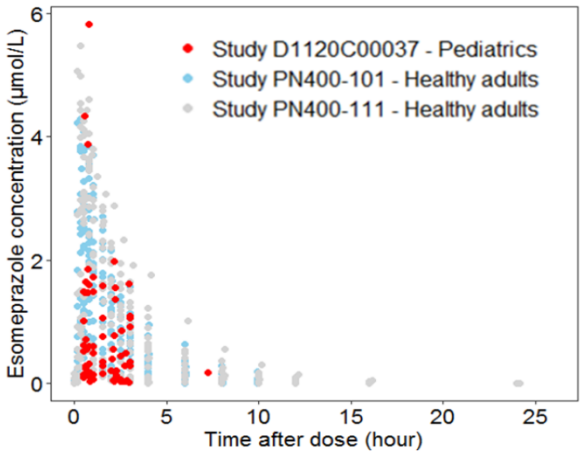
Plasma concentrations of esomeprazole from Vimovo observed in the adolescent JIA patients were comparable or in similar range as to the plasma concentrations of esomeprazole from Vimovo in healthy adults following multiple dosing (Figure 4 and Figure 5). Although most of the observed esomeprazole concentrations in JIA adolescent patients were in lower end of the concentrations that were observed in healthy adults, this could be due to limited PK sampling around $C_{max}$ in combination with a high variability of PK in JIA pediatric patients.

*Figure-4: PK profiles of esomeprazole in JIA patients (A) and in healthy adults (B & C) after multiple doses of Vimovo BID*




Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Figure 1

*Figure-5: Overlay of Esomeprazole concentration profiles in the pediatric and adult studies*




Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Figure 2

One adolescent patient in study 037 had slightly higher esomeprazole concentration (5.82 umol/L) than that of adult. This subject (Subject # E7802006), appear to be in lower age range with lighter body weight (12 years of age with 37 kg body weight) in the studied population which may explain the observed higher esomeprazole concentration. Nevertheless due to the limited number of patients (n=1) for this observation, a definitive conclusion cannot be drawn.

**B:** *$C_{max}$ Comparison:*
As only one or two PK blood samples were collected per subject in this study 037, traditional non-compartmental PK analysis was not feasible for JIA adolescent patients. Only three adolescent subjects had relatively rich (four) PK samples to approximate the $C_{max}$. The observed $C_{max}$ in these three adolescent patients, although within the adult ranges, were in the lower range of what was found in the adult studies (See Appendix). This observation was consistent with what was seen in overall esomeprazole (Vimovo) plasma concentration comparison between the adolescent JIA patients and healthy adults in Figure-6. However, due to the sparseness of the PK sampling (only 4 samples/subject) even in these three subjects, these observed $C_{max}$ in adolescent JIA patients may not present the true $C_{max}$. Therefore, this $C_{max}$ comparison may not be reliable.

**C:** *Population PK Analysis:*
Adult esomeprazole data from Vimovo following multiple doses (Study PN400-101 & PN400-111) with intensive PK sampling were utilized to develop population PK model using nonlinear mixed effects modeling (NONMEM). According to the applicant, initial attempts to utilize both adult and pediatric Vimovo esomeprazole data to develop population PK model were unsuccessfu and it may be due to large inter-subject variability and relative sparseness of the adolescent data. A one-compartmental model with first-order absorption with lag-time to absorption phase best described the data. The developed adult PK model was scaled to pediatric patients by using allometric scaling with the fixed power exponent to address effects of body size on esomeprazole PK. Weight exponents of 0.75 for CL/F and 1.0 for V/F were applied to take into account body size differences in subjects as presented below:

$$CL_{pediatric} = CL_{adult} * \left(\frac{WT}{70}\right)^{0.75} \qquad V_{pediatric} = V_{adult} * \left(\frac{WT}{70}\right)^{1.0}$$

where: WT, represents body weight in kg.

Subsequently, *post-hoc* Empirical Bayes Estimated (EBEs) approach was used to estimate individual PK parameters oral clearance (CL/F) and volume of distribution (V/F) for the JIA adolescent patients based on their observed plasma concentration. Individual AUCs were estimated according to: AUCs = DOSE/(CL/F).

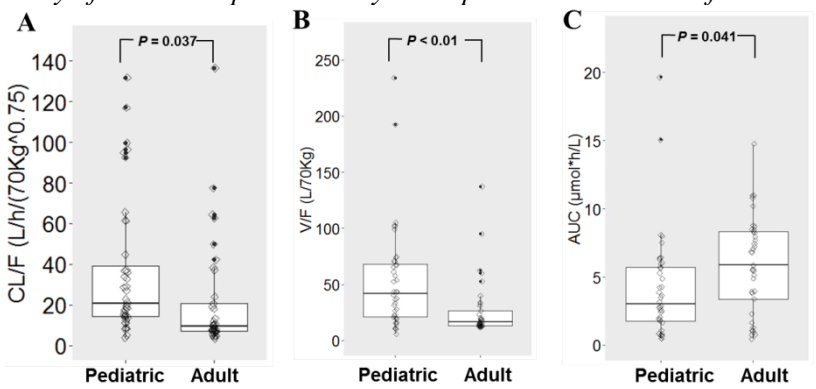
*Table-6: Summary of Individual Bayes PK Parameter Estimates for Esomeprazole*

| | Adolescents (D1120C00037; n = 40) | | Adults (PN400-101 & PN400-111; n = 37) | | |
|---|---|---|---|---|---|
| | Geometric mean | Median (Range) | Geometric mean | Median (Range) | p value |
| CL/F, L/h/70kg$^{0.75}$ | 24.66 | 20.57 (3.84 – 131.91) | 12.79 | 9.36 (3.43 – 136.62) | 0.037 |
| V/F, L/70kg | 38.68 | 41.95 (5.68 – 234.19) | 21.03 | 16.62 (11.77 – 137.36) | < 0.01 |
| AUC, μmol*h/L | 2.84 | 3.01 (0.51 – 19.68) | 4.39 | 5.87 (0.46 – 14.68) | 0.041 |

Abbreviations: CL/F, apparent clearance; V/F, apparent volume of distribution; AUC, area under the curve.

Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Table 7

*Figure-6: Summary of individual post-hoc Bayes PK parameter estimates for Esomeprazole*




Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Figure 4

This population PK analysis was re-analyzed by the agency using NONMEM and results were consistent with applicant's reported results.

Although the estimated individual esomeprazole CL/F and AUC in adolescent were generally within the range that was observed in adult, the estimated geometric mean of CL/F and V/F in adolescent were higher than those of adults, and thus the estimated geometric mean of AUC in adolescent were lower than that of adult (Table-6 and Figure-6).

> *Caveat of the Population PK analysis:*
> Sparse PK samples in study 037 were only collected to up to 3 hrs post-dose in JIA adolescent patients where $t_{max}$ of immediate release of esomeprazole from Vivomo was around 0.5 hr and half-life is around 1-1.5 hrs following multiple dosing in healthy subjects. This limited PK sampling only to early time point in JIA adolescent patient could lead to the observed higher estimates of CL/F and consequently lower estimates of AUC in JIA patients compared to those in the adult studies which had multiple measurements at later time points up to 24 hours post-dose.

**D:** *Prior Experience:*

Nonetheless, from prior experience, delayed release esomeprazole PK from Nexium in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic

GERD (Table-7). The difference in formulation (IR in Vimovo vs. DR in Nexium) may affect the absorption phase of the esomeprazole PK. However, the clearance of esomeprazole is not anticipated to be impacted by the formulation difference.

*Table-7: Comparison of PK Parameters in 12 to 17 Year Olds with GERD and Adults with Symptomatic GERD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

| | 12 to 17 Year Olds (N=28) | | Adults (N=36) | |
|---|---|---|---|---|
| | **20 mg** | **40 mg** | **20 mg** | **40 mg** |
| AUC (µmol·h/L) | 3.65 | 13.86 | 4.2 | 12.6 |
| $C_{max}$ (µmol/L) | 1.45 | 5.13 | 2.1 | 4.7 |
| $t_{max}$ (h) | 2.00 | 1.75 | 1.6 | 1.6 |
| $t_{½λz}$ (h) | 0.82 | 1.22 | 1.2 | 1.5 |

Data presented are geometric means for AUC, $C_{max}$ and $t_{½λz}$, and median value for $t_{max}$.

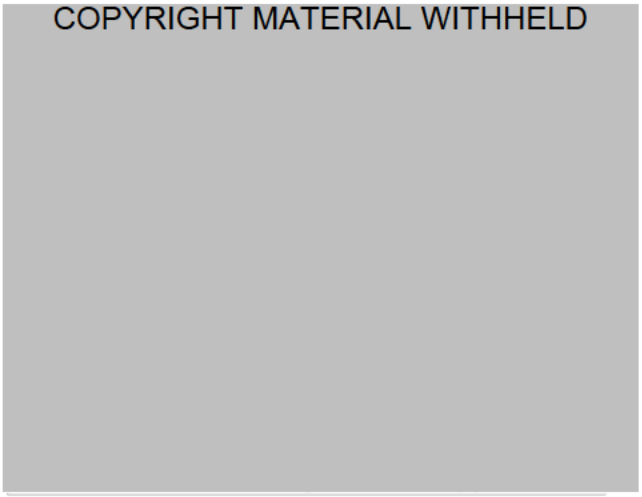
Source: Nexium Prescription label

### 2.2.3.2 Comparison with Adolescent with Delayed Release Esomeprazole Nexium

*Li et al. 2006* (which was utilized in Nexium labeling for adolescent as above in Table 6) reports mean esomeprazole PK data in GERD adolescent patients following single and multiple QD dosing of 20 mg and 40 mg Nexium, a delayed release product of esomeprazole.

As observed in Figure-7, the majority of the observed concentrations of IR esomeprazole (20 mg) from Vimovo following BID multiple dosing (40 mg total daily dose) in adolescent JIA patients in study 037 are in comparable range as concentrations of 40 mg DR esomeprazole from Nexium following QD multiple dosing (40 mg QD dosing) in GERD adolescent patients. This observation is supportive of the safety of proposed dose of Vimovo for esomeprazole component in pediatric JIA patients since 40 mg Nexium QD dosing is approved in adolescent patients.

*Figure-7: Esomeprazole concentrations in JIA patients administered with VIMOVO overlaid with averaged concentrations in adolescents with GERD administered with delayed release esomeprazole*




Li J, Zhao J, Hamer-Maansson JE, Andersson T, Fulmer R, Illueca M, Lundborg P. Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: A randomized, open-label study. Clin Ther 2006; 28: 419-27.

Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Figure 5

### 2.2.4 What is the recommended dose in adolescent patients with JIA based on the result of this study?

Initially, the applicant did not propose any specific dosing recommendation in the adolescent patient as they did not seek any additional indication in adolescent patient at the time of the submission.

However, based on the comparability of plasma exposure of both naproxen and esomeprazole components of Vimovo between the adults and adolescent at the studied doses in this submitted study, the FDA has concluded that it is reasonable to extrapolate the efficacy of Vimovo from adults to adolescent with JIA at the studied doses. The evaluated doses of Vimovo in the submitted adolescent study were weight based as following:

*Table 8: Vimovo doses by Body Weight in Study 037*

| Weight at Enrollment (kg)[1] | Minimum Dose[2] | Maximum Dose[2] |
|---|---|---|
| <38 | 250 mg / 20 mg | 250 mg / 20 mg |
| 38 – <50 | 250 mg / 20 mg | 375 mg / 20 mg |
| 50 – <75 | 375 mg / 20 mg | 500 mg / 20 mg |
| ≥75 | 500 mg / 20 mg | 500 mg / 20 mg |

[1] Based on typical day-to-day fluctuations in body weight, a ±3% window was permitted and used at the discretion of the Investigator when assigning the initial dose group.
[2] Study drug (VIMOVO, naproxen/esomeprazole magnesium) dose, divided twice daily (BID).

However, since 250 mg naproxen/20 mg esomeprazole of Vimovo is not an approved marketed strength in adults and the applicant did not seek marketing of this new strength in this submission, the FDA recommends that the use of Vimovo be limited to adolescent patients who weight 38 kg or greater. In addition, since the approved Vimovo dose in adult patients is to use the lowest effect dose of 375 mg or 500 mg naproxen without any specification of body weight, restricting adolescent patient who weighs 75 kg or greater to only 500 mg naproxen/20 mg esomeprazole of Vimovo may not be necessary. Therefore, we recommend the following dosing regimen for JIA in pediatric patients 12 years of age and older and weighing at least 38 kg:

- Baseline weight of 38 kg to <50 kg: 375 mg/20 mg tablets BID
- Baseline weight of > 50 kg: either 375 mg/20 mg or 500 mg/20 mg tablets BID

This dose recommendation is in line with studied doses in study D1120C00037, as well as applicant's proposal in a response to FDA information request (IR) dated March 24, 2017.

Currently, the approved dose of naproxen suspension for JA is 10 mg/kg/day given in 2 divided doses according Naproxen label. Although the studied naproxen dose in Study 037 and our recommended dose of naproxen from Vimovo are higher than the currently approved dose of naproxen suspension in JA (table-9), observed plasma concentrations for naproxen from Vimovo in adolescent in Study 037 were generally within the observed concentration range in adults after 500 mg naproxen dose. The recommended doses are also within the clinical practice recommended naproxen dose of 10-20 mg/kg/day with a maximal daily dose of 1000 mg naproxen in adolescent patient according to "Textbook of Pediatric Rheumatology"[3]

*Table 9: FDA Recommended Vimovo Dose in Adolescent JIA patients by body Weight*

| Body Weight | FDA Recommended Dose | Body WT adjusted naproxen daily dose |
|---|---|---|

[3] Cassidy J, Petty RE, Laxer RM, Lindsley CB. Textbook of Pediatric Rheumatology. In, 2011.

| | | |
|---|---|---|
| 38-<50 kg | 375 mg/20 mg BID | 15-19.7 mg/kg/day |
| 50-<75 kg | 375 mg/20 mg BID | 10-15 mg/kg/day |
| | 500 mg/20 mg BID | 13.3-20 mg/kg/day |
| >75 kg | 375 mg/20 mg BID | 10 mg/kg/day |
| | 500 mg/kg BID | 13.3 mg/kg/day |

## 2.3 Analytical Section

### 2.3.1 What bioanalytical methods are used to assess concentrations of the measured moieties?

- Concentrations of naproxen in human plasma from study D1120C00037 were determined at BASi with a validated LC/MS/MS method titled "Quantification of Naproxen in Lithium Heparinized Human Plasma by LC-MS/MS" developed at (b) (4).
- Concentrations of esomeprazole in human plasma from study D1120C00037 were determined at (b) (4) using a validated LC/MS/MS method developed by (b) (4).

### 2.3.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? What are the lower and upper limits of quantification (LLOQ/ULOQ)?

| Analytes | Range of Standard Curve | LLOQ | ULOQ |
|---|---|---|---|
| Naproxen | 0.1 to 100 µg/mL (8 levels) | 0.1 µg /mL | 100 µg/mL |
| Esomeprazole | 20 to 20000 nmol/L (8 levels) | 20 nmol/L | 20000 nmol/L |

- The concentration of naproxen was calculated using a 1/concentration2 weighted quadratic regression of peak area ratio versus concentration. The standard curve range of naproxen from 0.1-100 ug/mL was appropriate as the observed $C_{max}$ in 4 subjects ranged between 32.4 and 82.8 ug/mL. The highest concentration measured in this study was 97.3 ug/mL, and 5 out of 94 analyzed samples were BLOQ.
- Concentration of esomeprazole was calculated using a linear regression ($1/x^2$ weighted). The standard curve range of esomeprazole from 20-20000 nmol/L was appropriate as the observed $C_{max}$ in 5 subjects with frequent PK sampling ranged between 916 and1720 nmol/L. The highest concentration measured in this study was 5820, and 21 out of 94 analyzed samples were BLOQ (20 nmol/L).

### 2.3.3 What are the accuracy, precision and selectivity at these limits?

| Analytes | QC precision | QC accuracy |
|---|---|---|
| Naproxen | 0% to 12.1% | -4.9% to 9.7% |
| Esomeprazole | 1.9% to 5.4% | -2.5% to 9.6% |

Both methods had adequate selectivity for determination for both naproxen and esomeprazole.

### 2.3.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Naproxen plasma samples were stored at approximately -20ºC until analysis and esomeprazole plasma samples were stored at approximately -10 to -30°C until analysis. All samples were analyzed within the time period for which the long-term stability has been established. The

maximum storage periods from sample collection through sample analysis were 691 days for naproxen in plasma and 587 days for esomeprazole in plasma.

| Analyte | Freeze-thaw -20°C (Cycles) | At Room temperature | At 4°C (autosampler) | Long term storage at -20°C |
|---|---|---|---|---|
| Naproxen | 6 | 27 hr | 1 day | 806 days |
| Esomeprazole | 5 | 26 hr | 100 hours | 729 days |

**2.3.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

- Naproxen: QC samples at 3 different concentrations (0.30, 8.0 and 80.0 µg/mL) of naproxen were prepared. At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. All of the incurred sample repeats (21 samples) met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being (b) (4) %.

- Esomeprazole: QC samples at 3 different concentrations (60.0, 900, and 16000 nmol/L) of esomeprazole were prepared. At least 25% (24 out of 94 samples) of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. All of the incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being (b) (4) %.

# 3 Appendix:

## 3.1 Individual Study Report:

**TITLE:** A 6-month, Multicenter, Open-label, Safety Study of VIMOVO (250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg Naproxen/Esomeprazole) in Adolescents Aged 12 to 16, Inclusive, with Juvenile Idiopathic Arthritis (JIA)

**STUDY D1120C00037**

**STUDY SITE:**

**Clinical Site:** US only, multicenter

**Analytical Site:** Naproxen: (b) (4)

Esomeprazole: (b) (4)

**PHASE OF STUDY:** Phase 4 study

**OBJECTIVE:**

- The primary objective of this study was to evaluate the safety and tolerability of VIMOVO in adolescent aged 12 to 16 years, inclusive, with JIA.
- The secondary objective was to evaluate the PK characteristics of VIMOVO in adolescents aged 12 to 16 years, inclusive, with JIA.
- The exploratory objective was to evaluate the signs and symptoms of JIA in adolescents aged 12 to 16 years, inclusive, receiving VIMOVO.

**Study Rationale:**

This study was conducted to fulfill the PMR for the treatment of JIA in adolescents as required under the FDA PREA1634-2.

**STUDY DESIGN:**

This was a Phase 4, US only, multicenter, open-label, single arm, non-comparator study designed to evaluate the safety of VIMOVO (250 mg/20 mg, 375 mg/20 mg, or 500 mg/20 mg naproxen/esomeprazole) in the treatment of JIA in adolescent patients for up to 6 months to fulfill a FDA Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) 1634-2.

Treatment period with open-label VIMOVO was up to 6 months with a 2-week follow-up period for assessment of safety

**Doses:**

250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg, naproxen/esomeprazole magnesium

The VIMOVO strength for each patient was determined by the patient's weight at baseline and the Investigator's discretion according to published clinical guidelines for naproxen use (Cassidy 2011). The target dose of the naproxen component was within the range of 10-20 mg/kg/day divided twice daily (BID) with a maximum daily dose of 1000 mg.

- Baseline weight <38 kg: 250 mg/20 mg tablets BID
- Baseline weight of 38 kg to <50 kg: either 250 mg/20 mg or 375 mg/20 mg tablets BID
- Baseline weight of 50 kg to <75 kg: either 375 mg/20 mg or 500 mg/20 mg tablets BID
- Baseline weight ≥75 kg: 500 mg/20 mg BID

The tablets were taken whole, orally, and swallowed whole with liquid on an empty stomach at least 30 minutes before the morning and evening meals. Tablets were not to be split, chewed, crushed, or dissolved.

*Reviewer's Comment: The way the Vimovo tablet was administered in this study is consistent with the recommendation in the Vimovo label.*

**Study Population:**

Male and non-pregnant female patients age 12 to 16 years diagnosed with JIA. A total of 46 patients were enrolled and dispensed study drug. Thirty-six patients completed 6 months of study drug treatment, and 10 patients discontinued prematurely (4 because of AEs, 1 because of severe protocol noncompliance, 2 were lost to follow-up, and 3 withdrew consent).

Therefore, 46 patients were included in the analysis of safety, 44 patients were included in the analysis of efficacy, and 42 patients were included in the PK population. Those patients in the PK population who had samples with measurable concentrations were included in the analysis of PK: 40 patients for esomeprazole and 41 patients for naproxen.

*Table 1: Patient Disposition (All Patients)*

| | Number (%) of Patients[1] | | | |
|---|---|---|---|---|
| | **VIMOVO 250 mg/20 mg** | **VIMOVO 375 mg/20 mg** | **VIMOVO 500 mg/20 mg** | **Total** |
| Enrolled[2] | | | | 51 |
| Not assigned treatment (eligibility criteria not fulfilled) | | | | 5 |
| Assigned treatment | 4 | 20 | 22 | 46 |
| Received study drug | 4 (100) | 20 (100) | 22 (100) | 46 (100) |
| Completed study[3] | 3 (75.0) | 16 (80.0) | 17 (77.3) | 36 (78.3) |
| Completed study and received 6 months of study drug[4] | 3 (75.0) | 16 (80.0) | 17 (77.3) | 36 (78.3) |
| Discontinued prematurely | 1 (25.0) | 4 (20.0) | 5 (22.7) | 10 (21.7) |
| Adverse event | 1 (25.0) | 1 (5.0) | 2 (9.1) | 4 (8.7) |
| Lost to follow-up | 0 | 2 (10.0) | 0 | 2 (4.3) |
| Severe non-compliance with protocol | 0 | 1 (5.0) | 0 | 1 (2.2) |
| Withdrawal by patient | 0 | 0 | 3 (13.6) | 3 (6.5) |

**Key exclusion criteria:**

- Patient had estimated baseline creatinine clearance of <60 mL/minute

  The Schwartz equation was used to calculate the glomerular filtration rate (GFR) in children from serum creatinine, which uses serum creatinine and the child's height to estimate GFR as follows (Schwartz 2009; Schwartz and Work 2009):

  $$eGFR = k\ x\ height/serum\ creatinine$$

  where k was a constant that depended on muscle mass (k = 0.413)

- Patient had severe hepatic impairment (e.g., Child-Pugh C score).
- Patient had known hypersensitivity to naproxen, esomeprazole, substituted benzimidazoles, or to any of the excipients.

*Reviewer's Comment: The key exclusion criteria were reasonable based on the current label for Vimovo.*

**Concomitant Therapy**
Use of the following drugs was prohibited during the study:
- Treatment with another NSAID including additional naproxen at enrollment and during the study. NSAIDs, other than the study drug (VIMOVO), were prohibited during the study.
- Continuous treatment with antacids, H2 -receptor antagonists, or PPIs, in addition to the VIMOVO (esomeprazole) received during this study.
- Continuous treatment with antifungals, antiretroviral drugs (atazanavir, nelfinavir, saquinavir), cilostazol, or warfarin (Coumadin®) or the use of these agents at any time between Visit 1 (Screening visit) and the final study visit (Visit 8 or ET visit).

**Efficacy:**
Efficacy assessments, which were exploratory in nature, were collected at baseline and at Months 1, 3, and 6 of the treatment period.
- Physician's global assessment of disease activity
- Childhood Health Assessment Questionnaire (CHAQ):
    - Functional area scores (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities)
    - Disability index
    - Global assessment of overall well-being index
    - Discomfort index
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- American College of Rheumatology (ACR) Pediatric response, derived from the following:
    - Physician's global assessment of disease activity
    - CHAQ global assessment of well-being
    - CHAQ disability index score
    - Number of joints with active arthritis
    - Number of joints with limited range of motion
    - Serum CRP or ESR

**Pharmacokinetic Measurements:**
PK Blood Samples:

The PK sampling was conducted when the exposure to naproxen and esomeprazole were at steady state. Both esomeprazole and naproxen levels were determined in all PK samples.
Blood samples for determination of naproxen and esomeprazole plasma concentrations were collected as follows:
- Frequent sampling (Month 1 only) for **up to 8 patients**: samples obtained prior to morning dose intake and at 0.5, 1, 1.5, and 3 hours (±5 minutes) following morning dose intake on Month 1 (day 23-37).

- Sparse sampling (Months 1 and 3): a single sample from remaining patients who did not participate in frequent sampling, at Months 1 (Day 23-37) and 3 (Day 83-97). The sample was obtained 0.5 to 1 hour following intake of the morning dose at 1 of these visits and between 2 to 3 hours following intake of the morning dose at the other visit.

Blood samples were frozen (-20°C or below) and transported to the relevant laboratory and kept frozen at all times.

**Bioanalytical Analysis:**
Blood samples were frozen (-20°C or below) and transported to the relevant laboratory and kept frozen at all times.

**Naproxen:**

- Concentrations of naproxen d in human plasma were determined at (b) (4) with a validated LC/MS/MS method titled "Quantification of Naproxen in Lithium Heparinized Human Plasma by LC-MS/MS" developed at (b) (4) A total of 94 bioanalytical project samples were assayed.
- The standard curve for naproxen with 8 concentration levels range from 0.100 to 100 µg/mL with a lower limit of quantitation (LLOQ) of 0.1 µg/mL, and was calculated using a 1/concentration2 weighted quadratic regression of peak area ratio versus concentration. The average $R^2$ was 0.9968.
- Quality Control (QC) samples at 3 different concentrations (0.30, 8.0 and 80.0 µg/mL) of naproxen were prepared.
- The inter-assay coefficients of variation of the QCs for the naproxen runs ranged from 2.0% to 12.1%, with mean percent differences from theoretical ranging from -4.9% to 9.7%.
- The differences of back-calculated calibration curve values from nominal values ranged from -1.6% to 1.2%for naproxen.
- At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. All of the samples (21 of 21 samples demonstrated a percent difference within ±20.0%, which meets the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -20°C until analysis, were analyzed within the time period for which the long-term plasma stability naproxen has been established.
    - The study was conducted between 04/12/2012 (date of first enrolment) through 02/03/2015 (date of last patient contact).
    - Plasma samples were collected between 07/12/2012 (first PK sample collection) through 10/30/2014 (last PK sample collections)
    - Plasma samples were received between 10/10/2012 through 11/14/2014.
    - Plasma samples were analyzed between 05/09/2013 through 12/02/2014.
    - The maximum storage period from collection through analysis was 691 days.
    - The long term storage stability of naproxen in human plasma at -20 °C was established for at least for 806 days.
    - Maximum number of freeze/thaw cycles in this bioanalytical project was 3 cycles where the validated freeze/thaw stability of naproxen was at least 6 cycles at -20°C.

*Method Validation:*
*Validation for quantification of naproxen in sodium heparinized human plasma by LC-MS/MS was validated in February 2009 by* (b) (4)*. Additional 3 addendum were added on January 2010, November 2011, May 2012.*

*Table 2: Naproxen Bioanalytical Method Validation*

| Parameter | | Naproxen | Units |
|---|---|---|---|
| Calibration standard range | Upper limit | 100 | µg/mL |
| | Lower limit | 0.100 | µg/mL |

| | | | |
|---|---|---|---|
| Quality control sample range | High<br>Middle<br>Low | 80.0<br>8.00<br>0.300 | µg/mL<br>µg/mL<br>µg/mL |
| Freeze/thaw stability | At -20±10°C | 6 | cycles |
| | At -80±10°C | 4 | cycles |
| Freeze/thaw stability with co-administered drug Omeprazole | At -20±10°C | 6 | cycles |
| | At -80±10°C | 6 | cycles |
| Short term stability in matrix | At ambient conditions | 27 | hours |
| Long term stability in matrix | At -20±10°C<br>At -80±10°C | 300<br>127 | days<br>days |
| Long term stability in matrix with co-administered drug Omeprazole | At -20°C<br>At -80°C | 806<br>806 | days<br>days |
| Processed sample stability | At ambient conditions | 79 | hours |
| Reinjection reproducibility | At ambient conditions | 26 | hours |
| Analyte and internal standard stock solution stability | At 2-8°C | 35 | days |
| Analyte and internal standard stock solution stability | At ambient conditions | 6 | hours |
| Internal standard working solution stability | At 2-8°C | 1 | day |
| Internal standard working solution stability | At ambient conditions | 25 | hours |
| Whole blood stability | At ambient conditions | 2 | hours |
| Extraction efficiency | | 90.8%<br>77.7% | Naproxen<br>ISTD |
| Matrix effect | | -6.0%<br>-5.6% | Naproxen<br>ISTD |
| Selectivity | 6 sources | No interferences | |

**Esomeprazole:**

- Concentrations of esomeprazole in human plasma were determined at [redacted] (b) (4) using a validated LC/MS/MS method developed by [redacted] (b) (4) A total of 94 samples were analyzed.
- Calibration standard curve consisted of 8 level ranged from 20.0 to 20000 nmol/L in human plasma, with an LLOQ of 20 ng/mL, and was calculated using a linear regression ($1/x^2$ weighted). The average $R^2$ was 0.9975.
- QC samples at 3 different concentrations (60.0, 900, and 16000 nmol/L) of esomeprazole were prepared
- The inter-assay coefficients of variation of the QCs for the esomeprazole runs ranged from 1.9% to 5.4%, with mean percent differences from theoretical ranging from -2.5% to 9.6%.
- The differences of back-calculated calibration curve values from nominal values ranged from -5.0 to 5.6%.
- At least 25% (24 out of 94 samples) of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. All of the incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.

- Plasma samples, stored at approximately -10 to -30°C were analyzed within the time period for which the long-term stability of plasma omeprazole has been established.
  - The study was conducted between 04/12/2012 (date of first enrolment) through 02/03/2015 (date of last patient contact).
  - Plasma samples were collected between 07/12/2012 (first PK sample collection) through 10/30/2014 (last PK sample collections)
  - Samples were received from 10/19/2012 through 2/12/2014 for study 8259652 and from 04/19/2014 through 11/12/2014 for study 8297708.
  - Plasma samples were analyzed between 02/08/2013 through 11/20/2014.
  - The maximum storage period from collection through analysis was 587 days.
  - The long term storage stability of omeprazole in human plasma was established for 729 day at -10 to -30 °C and 280 days at -60 to -80 °C.

*Method Validation:*
*Validation for quantification of esomeprazole in human plasma by HPLC-MS/MS was validated in March 2012 by* (b) (4). *Additional addendum No 2 dated October 19, 2016 was provided later.*

This method is not enantiomer specific and both esomeprazole and omeprazole can be quantitated using calibration standards and quality control (QC) samples prepared with omeprazole.

*Table 3: Esomeprazole Bioanalytical Method Validation*

| **Parameter** | | **Omeprazole** | **Units** |
|---|---|---|---|
| Calibration standard range | Upper limit | 20.0 | nmol/mL |
| | Lower limit | 20000 | nmol/mL |
| Quality control sample range | High | 16000 | nmol//mL |
| | Middle | 900 | nmol/mL |
| | Low | 60 | nmol//mL |
| | Low | 20 | nmol//mL |
| Freeze/thaw stability | At -10 to -30°C | 5 | cycles |
| | At -60 to -80°C | 5 | cycles |
| Short term stability in matrix | At Room Temperature | 26 | hours |
| Long term stability in matrix | At -10 to -30°C | 729 | days |
| | At -60 to -80°C | 280 | days |
| Processed sample stability | At 2-8°C | 100 | hours |
| Stability of standard stock solution | At room temperature | 6 | hours |
| Stability of intermediate solution | At room temperature | 6 | hours |
| Whole blood stability | Room Temp & on wet ice | 2 | hours |
| Matrix effect | | 4.0% | Omeprazole |
| | | 3.2% | ISTD |
| Selectivity | 6 sources | No interferences | |

- Acceptable selectivity for the determination of omeprazole, in the presence of naproxen, acetylsalicylic acid and salicylic acid was demonstrated.
- No carry over effect.

**RESULTS:**

**Naproxen PK:**

$C_{max}$ Comparison:
The applicant did not conduct population PK analysis for naproxen component due to sparse nature of the PK sampling data. Only $C_{max}$ values were compared between the pediatric population and adults. Of the 41 patients, only 4 patients, three subjects who took VIMOVO 500 mg naproxen BID (# 7820003, 7820004 and 7821001) and one subject who took VIMOVO 250 mg naproxen (# 7821002) had more than two PK samples that allowed the estimation of $C_{max}$ and $T_{max}$.

$C_{max}$ of EC-naproxen from Vimovo occurs at approximately 4-6 hours in adults following single dose administration and at approximately 3-4 hours following multiple-dose administration. $T_{max}$ of EC-naproxen from EC-NAPROSYN is also around 4 hours after multiple doses. However, in this pediatric study, PK samples were only collected up to 3 hours post-dose, while $C_{max}$ may not be reached. In these 4 subjects with estimated $C_{max}$, PK samples were not collected after $T_{max}$ to demonstrate a decline in plasma concentration. Therefore, the estimated $C_{max}$ for the pediatric population in this study may not be reliable due to limited PK sampling. In addition, the $C_{max}$ was only estimated for 4 subjects (3 subjects at 500 mg and 1 subject at 250 mg) resulting in unreliable $C_{max}$ comparison between adolescent and adults.

*Table 4: Naproxen $C_{max}$ and $T_{max}$ Estimates in Pediatric Patients in the VIMOVO 250 mg/20 mg (naproxen/esomeprazole) Treatment Group*

| Patient Number | E7821001 | Pediatric Data[1] Mean (range) N=12 | Adult Values[2] Mean (range) |
|---|---|---|---|
| Age (years) | 13.6 | 13.0 (8.1 – 14.1) | 31 (18-53) |
| Body weight (kg) | 43 | 42.1 (33.0 – 52.0) | 72 (55.1-99.8) |
| $T_{max}$ (hours) | 1.5 | 2.7 (1.0 – 8.0) | 4.03[3] (2-16.25) |
| $C_{max}$ (µg/mL) | 46.9 | 68.5 (47.0 -95.1) | 37.1 (23.4-51.4) |

[1]Wells TG, Mortensen ME, Dietrich A, Walson PD, Blasier D, Kearns GL. Comparison of the pharmacokinetics of naproxen tablets and suspension in children. J Clin Pharmacol. 1994;34(1):30-3. (PK was collected up to 24 hours)
[2]Adult values were observed from an adult pharmacokinetic study (Study D1120C00040) in 28 healthy volunteers following single dose administration.

Pediatric data in in Wells et al study with 250 mg naproxen dose was obtained with IR naproxen following a single dose administration with PK sampling for up to 24 hours post-dose. However, this current pediatric study was conducted with enteric coated naproxen in Vimovo and PK samples were collected only up to 3 hours post-dose following multiple dose administration. Therefore, the naproxen pediatric $C_{max}$ comparison in table-4 is not a fair comparison.

*Table 5: Naproxen $C_{max}$ and $T_{max}$ Estimates in Pediatric Patients in the VIMOVO 500 mg/20 mg (naproxen/esomeprazole) Treatment Group*

| Patient Number | Patient E7820003[1] | Patient E7820004[1] | Patient E7821001[1] | Mean ± SD[1] | NAPROSYN[2] (mean, CV) Day 7 | EC-NAPROSYN[2] Day 7 | Vimovo (500mg/20 mg) Single dose[3] | Vimovo (500mg/20 mg) Day 14[3] |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | 15.3 | 13.5 | 13.1 | 14.0 ± 0.9 | Adults | Adults | Adults | Adults |
| **BW (kg)** | 62 | 55 | 59 | 58.7 ± 2.9 | - | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **$T_{max}$ (hours)** | 3.0 | 1.5 | 1.02 | 1.8 ± 0.8 | 1.9 (61%) | 4 (39%) | 6.15 (58%) | 3.63 (64%) |
| **$C_{max}$ (µg/mL)** | 82.8 | 32.4 | 40.5 | 51.9 ± 22.1 | 97.4 (13%) | 94.9 (18%) | 66.9 (22%) | 80.5 (28%) |

1 Individual Pediatric patients are from the JIA Study D1120C00037.
2 Obtained from the FDA approved drug label for NAPROSYN®.
3 Vimovo Clinical Pharmacology Review

Exposure Comparison with Precious Pediatric and adult data:

*Table 6: Study Design Differences between Pediatric JIA Study and Healthy Adult Subjects Study*

| Description | Pediatric study (D1120C00037) | Adult study (PN400-104) | Adult study (PN400-105) | Healthy Adult (D1120C0040 | Pediatric study Naproxen suspension (Ansell et al. 1975) | Pediatric study Naproxen suspension (Valitalo et al.2012) |
|---|---|---|---|---|---|---|
| Number of patients | n = 41 | n = 28 | n = 30 | N= 28 | n = 9 | n = 53 |
| Age range | 12-17 years | 18-34 years | 19-54 years | 18-53 years | 5-14 years | 0.25-12 years |
| Dosage | 250 mg/20 mg, 375 mg/20 mg, 500 mg/20 mg naproxen/ esomeprazole depending upon body weight | 500 mg/20 mg naproxen/ esomeprazole | 375 mg/20 mg naproxen/ esomeprazole | 250 mg/20 mg naproxen/ esomeprazole | 5 mg/kg naproxen suspension; dose range 122.5 – 250 mg | 10 mg/kg naproxen suspension; |
| Dosing frequency | Multiple doses | Multiple doses | Single dose | Single dose | Single dose | Single dose |
| Time of PK sampling | Month 1 & 3 | Day 9 | Day 1 | Day 1 | Day 1 | Day 1 |
| Food intake | Not specified | Fasted | Fasted | Fasted | Not specified | Not specified |
| Sampling frequency | Mostly sparse (1-2 PK samples); 6 subjects contributing 3-4 PK samples | Rich sampling (28 PK samples per patient) | Rich sampling (20 PK samples per patient) | Rich sampling (20 PK samples per subject) | Post-dose 1, 2, 12 and 24 hours | 2-7 samples/patients between 13 minutes and 51 hours post-dose |
| Lower limit of quantification | 0.1 µg/mL | 0.1 µg/mL | 0.1 µg/mL | 25 nmol/L (8.635 ng/mL) | Not specified | Not specified |

**Figure 1. Naproxen concentrations from Study 037 compared to those in healthy adult subjects receiving 375 mg naproxen as Vimovo**

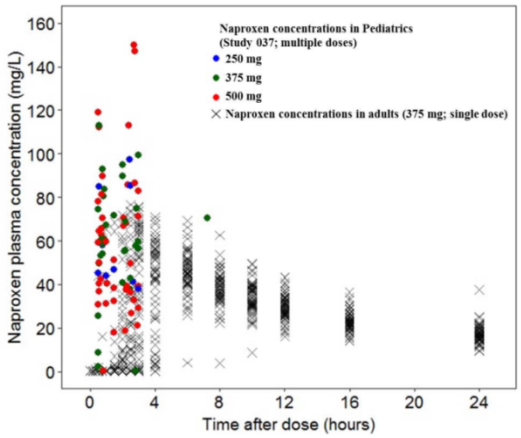



**Figure 2. Naproxen concentrations from Study 037 compared to those in healthy adult subjects receiving 500 mg naproxen as Vimovo**

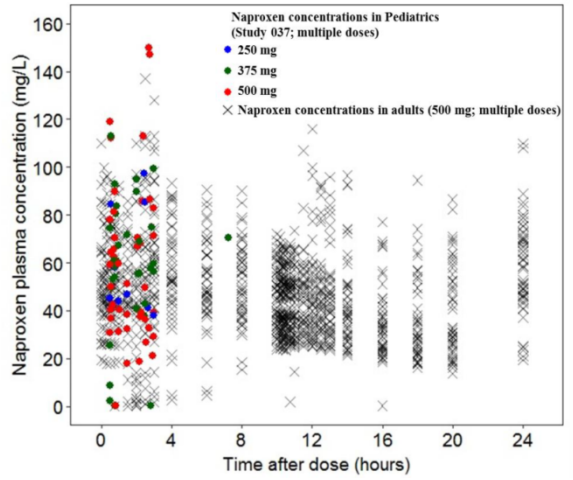



**Figure 3. Naproxen concentrations from Study 037 compared with the mean naproxen PK profile in pediatric patients who took the approved dose of naproxen for Juvenile Arthritis (5 mg/kg as naproxen suspension)**

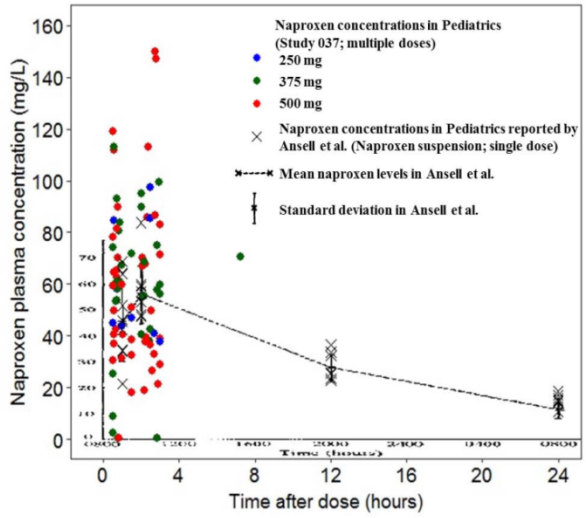
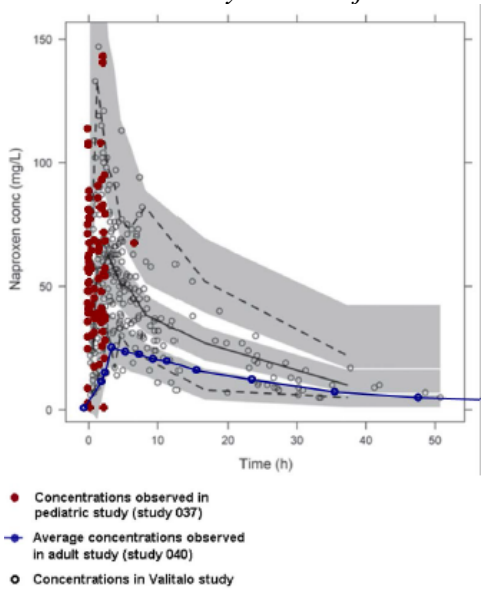


*Figure 4. Naproxen concentrations from Study 037 compared to Pediatric data from literature and those in healthy adult subjects receiving 250 mg naproxen as Vimovo*




Source: PK Report Addendum: Naproxen Data Analysis Figure 3
Pediatric study (037) = the current study in JIA patients (D1120C00037)
Adult study (040) = study D1120C0040 in healthy adults
Valitalo P, Kumpulainen E, Manner M, Kokki M, Lehtonen M, Hooker AC, et al. Plasma and cerebrospinal fluid pharmacokinetics of naproxen in children. J Clin Pharmacol. 2012;52(10):1516-26.

*The black line on the center represents median observed concentrations and the dotted black lines 2.5th and 97.5th percentile intervals for observations. The gray areas represent 95 % confidence intervals for 2.5th, 50th and 97.5$^{th}$ percentile prediction intervals.*

*<u>Reviewer's Comment:</u> In this plot, pediatric patients had received naproxen dose of 250 mg, 375 mg and 500 mg whereas the adult subjects had only 250 mg naproxen. Therefore, it is not a fair comparison.*

Conclusion for Naproxen:

- $C_{max}$ Comparison:
  - Unreliable $C_{max}$ estimation for naproxen due to limited PK sampling only up to 3 hour. In addition, the $C_{max}$ was only estimated for 4 subjects (3 subjects at 500 mg and 1 subject at 250 mg) resulting in unreliable $C_{max}$ comparison with adults.
  - Population PK may not be feasible for naproxen due to PK sampling limitation.
- Concentration Comparison:
  - The VIMOVO naproxen concentrations observed in the pediatric study (Study 037), regardless of naproxen dose (250 mg, 375 mg and 500 mg), are comparable to what has been previously observed in healthy adults who took 500 mg VIMOVO naproxen at steady state and in pediatric patient who tool 10 mg/kg naproxen suspension following single dose administration.
    - According to the EC-Naprosyn label, 5 mg/kg single dose naproxen suspension (recommended dose for pediatric JRA) in pediatric patients produced similar plasma exposure to those seen in adults taking 500 mg.
  - The VIMOVO naproxen concentrations in the pediatric study (Study 037) are higher than what was previously observed in healthy adults who took 250 mg and 375 mg naproxen as VIMOVO and in pediatric juvenile arthritis patients who took 5 mg/kg naproxen suspension. The differences in PK observations could be due to differences

in dosing regimens (single dose vs. multiple dose) as naproxen exposure accumulation after multiple days of dosing.

- There is approximately 1.70 to 2.63-fold increase in $AUC_{0\text{-}10am}$, which is more relevant to this study as the PK samples were collected following the morning dose in this study.
- There is approximately 1.2 to-1.5-fold accumulation in $AUC_{0\text{-}10,pm}$
- There is approximately 1.37 fold accumulation in $AUC_{0\text{-}24}$

**Esomeprazole PK:**

$C_{max}$ Comparison:

As only one or two PK blood samples were collected per subject in this study 037, traditional non-compartmental PK analysis was not feasible for JIA adolescent patients. Only three adolescent subjects had relatively richer (four) PK samples to approximate the $C_{max}$. The observed $C_{max}$ in these three adolescent patients, although within the adult ranges, were in the lower range of what was found in the adult studies (Table -7). This result was consistent with what was seen in overall esomeprazole (Vimovo) plasma concentration comparison between the adolescent JIA patients and healthy adults in Figure-6.

*Caveat:* However, due to the sparseness of the PK sampling (only 4 samples/subject) even in these three subjects, these observed $C_{max}$ in adolescent JIA patients may not present the true $C_{max}$. Therefore, this $C_{max}$ comparison may not be reliable.

*Table 7: Esomeprazole $C_{max}$ and $T_{max}$ estimates in pediatric patients*

| Patient Number | 377820003 (ID38) | 377820005 (ID40) | 377821001 (ID41) | Mean ± SD | Adult values* (Mean, range) |
|---|---|---|---|---|---|
| Age (year) | 15.3 | 13.7 | 13.1 | 14.0 ± 0.9 | 44, 22 – 65 |
| Body weight (kg) | 62 | 51 | 59 | 57.3 ± 4.6 | 73.9, 51.0 – 102.8 |
| $T_{max}$ (h) | 1.0 | 1.5 | 1.02 | 1.2 ± 0.2 | 0.51, 0.17 – 1.0 |
| $C_{max}$ (µmol/L) | 1.5 | 0.8 | 1.7 | 1.3 ± 0.4 | 3.11, 0.50 – 5.47 |

*Adult values were derived from an adult PK studies (study PN400-101 & PN400-111) in 37 healthy volunteers.

Comparison with Adolescent with Delayed Release Esomeprazole Nexium

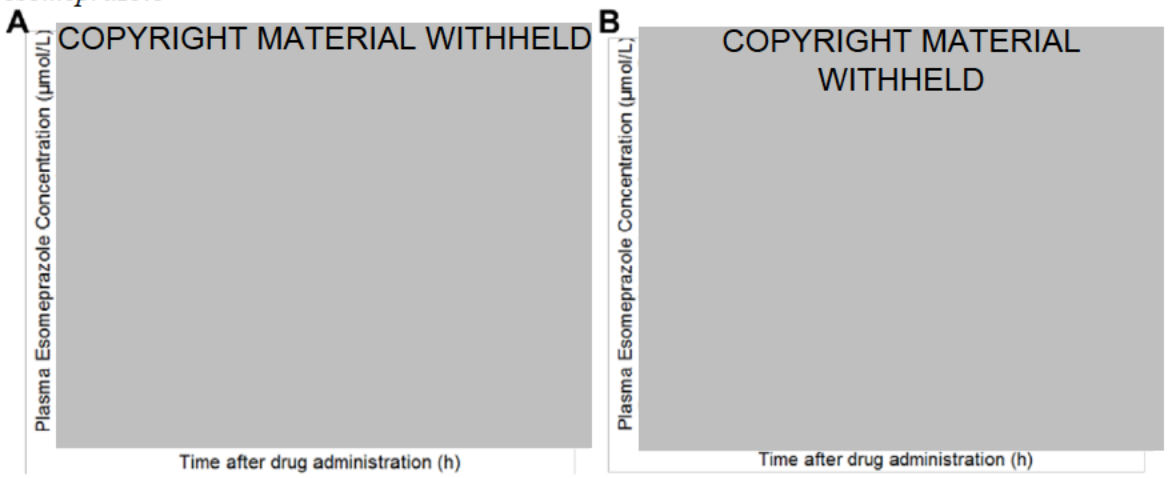
*Li et al. 2006*(which was utilized in Nexium labeling for adolescent) reports mean esomeprazole PK data in GERD adolescent patients following single and multiple QD dosing of 20 mg and 40 mg Nexium, a delayed release product of esomeprazole.

As observed in Figure-8, the majority of the observed concentrations of IR esomeprazole (20 mg) from Vimovo following BID multiple dosing (40 mg total daily dose) in adolescent JIA patients in study 037 are in comparable range as concentration of 40 mg DR esomeprazole from Nexium following QD multiple dosing (40 mg QD dosing) in GERD adolescent patients. This observation is supportive of the safety of proposed dose of Vimovo for esomeprazole component in pediatric JIA patients since 40 mg Nexium QD dosing is approved in adolescent patients.

However, the average estimated AUC in pediatric JIA patients who took 20 mg BID esomeprazole from Vimovo was slightly lower than adolescents who took 20 mg of Nexium QD (2.84 vs. 3.65 umol*h/L; Table-8) and about 5-fold lower than adolescent who took 40 mg Nexium QD. As mentioned in Section 2.2.3.1.C, this lower estimated AUC in pediatric JIA

patients could be a result of limited PK sampling only in early phase in study 037 which could cause the higher estimate of CL/F and consequently lower AUC in JIA patients.

*Figure 5: Esomeprazole concentrations in JIA patients administered with VIMOVO overlaid with averaged concentrations in adolescents with GERD administered with delayed release esomeprazole*




Li J, Zhao J, Hamer-Maansson JE, Andersson T, Fulmer R, Illueca M, Lundborg P. Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: A randomized, open-label study. Clin Ther 2006; 28: 419-27.

Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Figure 5

*Table 8: Esomeprazole population PK parameter estimates in current analysis compared to the literature*

| Study | Esomeprazole dosage (mg) | Administration Route | Formulation | Fasted | 1st or repeated doses | Number of subjects | Age range (years) | Analysis approach/ structure model | CL/F (L/h/70kg$^{*0.75}$) (Range or CV%) | V/F (L/70kg) (Range or CV%) | $AUC_{inf}$ (mean, 95% CI or CV% or range, umol*h/L) | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study D1120C00037 | 20 | Oral | immediate release (non-enteric coated) esomeprazole magnesium | Fasted; Foods allowed 30 mins after dose | Repeated | 40 | 12-16 | One-compt | 24.66 (3.84 – 131.91) | 38.68 (5.68 – 234.19) | 2.84 (0.51 – 19.69) | |
| Study PN400-101 & PN400-111 | 20 | Oral | immediate release (non-enteric coated) esomeprazole magnesium | Fasted; Foods allowed 60 mins after dose | Repeated | 37 | 22 - 65 | One-compt | 12.79 (3.43 – 136.62) | 21.03 (11.77 – 137.36) | 4.39 (0.46 – 14.68) | |
| Study PN400-101 & PN400-111 | 20 | Oral | immediate release (non-enteric coated) esomeprazole magnesium | Fasted; Foods allowed 60 mins after dose | Repeated | 37 | 22 - 65 | NCA | 12.43 (3.01 – 138.4) | 28.85 (10.25 – 602.03) | 4.52 (0.46 – 16.70) | |
| Hassan-Alin et al. 2000 [5] | 20 | Oral | Solution | Fasted | Repeated | 16 | Mean 28 years | NCA | NA | NA | 2.55 (1.94 - 3.36) | |
| Li et al. 2006 [4] | 20 | Oral | Capsule; delayed release | Fasted | Repeated | 12 | 12-17 | NCA | 18.26 (54) | NA | 3.65 (54) | GERD Patients |
| Li et al. 2006 [4] | 40 | Oral | Capsule; delayed release | Fasted | Repeated | 12 | 12-17 | NCA | 8.46 (39) | NA | 13.86 (39) | GERD Patients |

Abbreviations: One-compt, one compartment elimination model; NCA, non-compartmental analysis; CV, coefficient variation; CI, confident interval; CL/F, apparent clearance; V/F, apparent volume of distribution; AUC, area under the concentration-time curve; Oral, oral administration.

- Li J, Zhao J, Hamer-Maansson JE, Andersson T, Fulmer R, Illueca M, Lundborg P. Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: A randomized, open-label study. Clin Ther 2006; 28: 419-27.
- Hassan-Alin M, Andersson T, Bredberg E, Rohss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol 2000; 56: 665-70.

Source: Sponsor's VIMOVO Additional PK Analyses, Pharmacometrics Report dated 03/24/2017, Table 8

- Following single dose administration, IR esomeprazole from Vimovo has about 43% lower AUC compared to DR esomeprazole from Nexium (study PN 400-114). However, relative BA following multiple dosing with direct comparison with cross-over study design was not characterized in Vimovo application.

- Accumulation ratio (AUC) of esomeprazole following 5 days of dosing

| Adults (DR) | | Adult (IR) | Adolescent (DR) | |
|---|---|---|---|---|
| 20 mg QD | 40 mg QD | 20 mg BID | 20 mg QD | 40 mg QD |
| 1.9 | 2.6 | 3.8-5.8 | 2.46 | 2.46 |

Accumulation ratio based on $AUC_{0-24}$ following BID dosing was 3.8-fold when dose BID on day 1 though day 14 (including day 14) (study PN 400-101), and was 5.8 fold when Day 1 and 10 was QD and Day 2-9 was BID (study PN 400-111)

- Adolescent have similar PK to that of adults at both 20 mg at 40 mg following both single dose and multiple dose administration with delayed release (DR) formulation.

| Dose | SD/MD | subjects | AUC μmol·h/L | $C_{max}$ μmol/L | $T_{1/2}$ (hr) |
|---|---|---|---|---|---|
| 20 mg | Single Dose | Adult Healthy | *2.3* | *1.32* | 0.94 (44%) |
| | | Adult Healthy | 1.34 (1.02-1.77) | 1.86 (1.58-2.18) | 0.75 (0.58-0.91) |
| | | Adolescent GERD | 1.58 (63%) | 0.67 (176%) | 0.55 |
| | Multiple Dose | Adult Healthy | 2.55 (1.94-3.36) | 2.65 (2.26-3.11) | 1.01 (0.85-1.18) |
| | | Adult GERD | 4.2 (59%) | 2.1 (45%) | 1.2 |
| | | Adolescent GERD | 3.65 (54%) | 1.45 (12%) | 0.82 |
| 40 mg | Single dose | Adult Healthy | 4.32 (304-6.14) | 2.38 (1.77-3.19) | 0.85 (0.73-0.99) |
| | | Adolescent GERD | 5.57 (62%) | 2.78 (64%) | 0.86 |
| | Multiple Dose | Adult GERD | 12.6 (42%) | 4.7 (37%) | 1.5 |
| | | Adolescent GERD | 13.86 (39%) | 5.13 (45%) | 1.22 |

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