CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	22-511/S-019
Priority or Standard	Standard
Received Date(s)	June 7, 2016
PDUFA Goal Date	April 7, 2017
Division / Office	Division of of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)
Reviewer Name(s)	Marjorie F. Dannis, M.D. through Anil Rajpal, M.D.
Review Completion Date	February 26, 2016
Established Name	Naproxen/Esomeprazole Magnesium
Trade Name	Vimovo
Therapeutic Class	Combination NSAID and PPI
Applicant	Horizon Pharma, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	Naproxen (500 or 375mg) and Esomeprazole (20mg) twice daily
Indication(s)	Sponsor did not originally propose an indication; however, an indication may be granted (pending final review by Clinical Pharmacology and Pharmacometrics)
Intended Population(s)	Pediatric patients12 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Sponsor submitted the pediatric study report to fulfill the following PREA PMR:

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).1
A safety and population pharmacokinetic (PK) study in adolescents with JRA who are ages 12 years to 16 years 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.

In this efficacy supplement, the Sponsor proposed labeling to update the prescribing information to include the naproxen and esomeprazole pharmacokinetic and safety information resulting from that study. 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 (there was no indication proposed originally).

However, after review of the safety and PK[2] data, careful review of the regulatory history (See Section 2.5 below), and continued consultation with DPMH (and PeRC) it appeared that the totality of the data would support a pediatric indication. Thus, this medical officer recommends approval of the pediatric efficacy supplement and fulfillment of the above PREA PMR.

1.2 Risk Benefit Assessment

The current submission for Vimovo is a 505(b)(2) application using Nexium and EC Naprosyn as the reference listed drugs. Both of the reference listed drugs have been marketed in the United States for a number of years and have been used concurrently in patients at risk of developing ulcers due to chronic NSAID use. In addition, Vimovo is currently approved in adults for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers.

The current application was in response to the PREA PMR 1634-2 (shown above).

[1] Juvenile Rheumatoid Arthritis (JRA) is now called Juvenile Idiopathic Arthritis (JIA)

[2] It is this Reviewer's understanding that the preliminary determination by the Clinical Pharmacology and Pharmacometrics Reviewers is that the applicant's exposure matching approach is adequate; however, the final determination by the Clinical Pharmacology and Pharmacometrics Reviewers is pending at the time of this Review.

A six month safety and population pharmacokinetic (PK) study in adolescents (ages 12 - 16 years) with JIA who require treatment with NSAIDs was conducted. Demonstration of evidence of effectiveness is based on full extrapolation from adults, and is dependent on the adequacy of the applicant's exposure matching approach. It is this Reviewer's understanding that the preliminary determination by the Clinical Pharmacology and Pharmacometrics Reviewers is that the applicant's exposure matching approach is adequate; however, the final determination by the Clinical Pharmacology and Pharmacometrics Reviewers is pending at the time of this Review.

Although, at this time, there may not be a large population of adolescent JIA patients who require NSAID treatment for 6 months[3], there may be a subpopulation of patients who would benefit from treatment with this combination product, for example, those .patients who are unable to tolerate the newer disease-modifying anti-rheumatic drugs (DMARDs). To have additional treatment options for children with JIA and those who do not respond to other therapies would be beneficial. Pediatric health care providers may also welcome an additional alternative NSAID preparation that decreases GI toxicity and perhaps has less potential for adverse events.

Safety review by this medical officer did not reveal any new safety signals for Vimovo in this pediatric population. The safety of Vimovo is further supported by its approval in adults and the 6 years of safety data collected since the original approval in 2010. Thus, given the acceptable PK profile and acceptable safety profile, it is anticipated that the benefits of Vimovo treatment for relief of signs and symptoms of JIA in pediatric patients 12 years of age and older to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers, outweigh the risks.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

No new postmarketing risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarketing Requirements and Commitments

There are no additional recommendations for postmarketing requirements or commitments. In the opinion of this medical officer, the Sponsor has adequately addressed PREA PMR 1634-2 (see Section 1.1 above) with the current submission. Thus, this PMR should be considered fulfilled. (b) (4) there are no further outstanding PMRs.

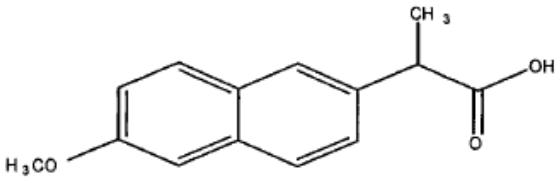
3 Beukelman T et al., "2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features." Arthritis Care & Research, April 2011, 63(4):465-582.

2 Introduction and Regulatory Background

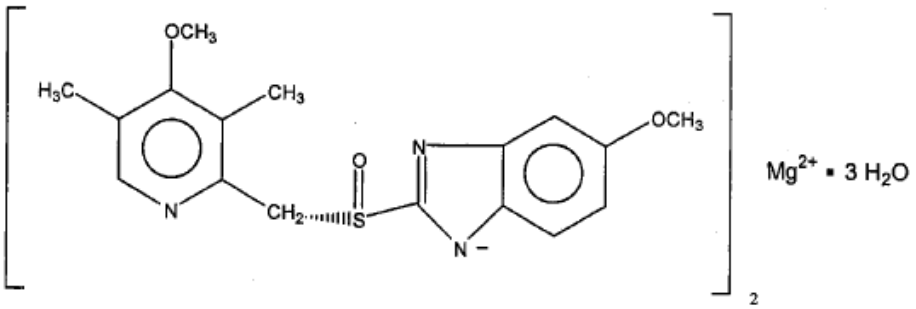
2.1 Product Information

Vimovo (naproxen and esomeprazole magnesium) is combination of a nonsteroidal anti-inflammatory drug and a PPI available as an oval, yellow, multi-layer, delayed-release tablet combining an enteric-coated naproxen core and an immediate-release esomeprazole magnesium layer surrounding the core. Each strength contains either 375 mg of naproxen and 20 mg of esomeprazole (present as 22.3 mg esomeprazole magnesium trihydrate) or 500 mg of naproxen and 20 mg of esomeprazole (present as 22.3 mg esomeprazole magnesium trihydrate) for oral administration. Following are the structural formulas for naproxen and esomeprazole magnesium respectively.

Naproxen - (*S*)-6-methoxy-α-methyl-2-napthaleneacetic acid



Esomeprazole magnesium – bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*- benzimidazole-1-yl) magnesium trihydrate



2.2 Tables of Currently Available Treatments for Proposed Indication

The sponsor did not originally propose an indication; however, an indication may be granted (pending final review by Clinical Pharmacology/Pharmacometrics) because:

Demonstration of evidence of effectiveness is based on full extrapolation from adults, and is dependent on the adequacy of the applicant's exposure matching approach. It is this Reviewer's understanding that the preliminary determination by the Clinical Pharmacology and Pharmacometrics Reviewers is that the applicant's exposure matching approach is adequate; however, the final determination by the Clinical Pharmacology and Pharmacometrics Reviewers is pending at the time of this Review.

Currently, there are no other available treatments for the potential indication in juvenile idiopathic arthritis (JIA) pediatric patients 12 years of age and older. It is theoretically possible for (JIA) pediatric patients 12 years of age and older to take an NSAID and a PPI separately. However, there is no combination product approved for this potential indication.

2.3 Availability of Proposed Active Ingredient in the United States

Both esomeprazole and naproxen have been marketed for a number of years in the United States. Pharmacologically, naproxen is a non-selective nonsteroidal anti-inflammatory drug that was first approved for marketing in the US in 1976. Naproxen is currently marketed in the US by several generic manufacturers and also under the trade names Naprosyn, EC-Naprosyn, Anaprox and Anaprox DS, and Alleve (OTC). It is indicated for the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis, acute gout. Some formulations are also indicated for the management of pain and primary dysmenorrhea.

Esomeprazole belongs to the class of anti-secretory compounds characterized pharmacologically as proton pump inhibitors. Esomeprazole is currently available in the U.S. as a prescription medicine for the treatment of symptomatic gastroesophageal reflux disease (GERD); short-term treatment in the healing and symptomatic resolution of erosive esophagitis; to maintain symptom resolution and healing of erosive esophagitis; the risk reduction of NSAID-associated gastric ulcer; *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; and the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Esomeprazole is currently marketed by generic manufacturers as well as under the trade name marketed Nexium[4].

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling of all NSAID products includes a Medication Guide and a Boxed Warning highlighting the potential for increased risk of cardiovascular events and the serious potentially life-threatening gastrointestinal bleeding associated with their use.

4 Nexium is also available as Nexium 24, an OTC product

The labeling of all PPIs contains various warnings and precautions, which over the last several years have increased in number. Below is the **WARNINGS AND PRECAUTIONS HIGHLIGHTS** section of the latest Vimovo label.

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- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4, 7)
- Heart Failure and Edema: Avoid use of VIMOVO in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of VIMOVO in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: VIMOVO is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue VIMOVO at first appearance of skin rash or other signs of hypersensitivity. (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs of symptoms of anemia. (5.11, 7)
- Masking of Inflammation and Fever: Potential for diminished utility of diagnostic signs in detecting infections. (5.12)
- Laboratory Monitoring: Obtain CBC and chemistry profile periodically during treatment. Monitor hemoglobin periodically in patients on long-term treatment who have an initial value of 10 g or less. (5.13)
- Active Bleeding: Withdraw treatment in patients who experience active and clinically significant bleeding. (5.14)
- Concomitant NSAID Use: Do not use VIMOVO with other naproxen-containing products or other non-aspirin NSAIDs. (5.15)
- Gastric Malignancy: In adults, symptomatic response to esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.16)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.17)
- *Clostridium difficile*-Associated Diarrhea: PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.18)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.19)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous, new

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Outlined below are highlights from presubmision regulatory activity as well as relevant regulatory activity from the current submission.

- Vimovo was originally approved in adults on April 30, 2010 for the following indications:
    - 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
- At that time, the agreed upon[5] recommendation for pediatric studies was:
    - "…comparative PK studies in pediatric patients >2 years of age with an age-appropriate formulation of Vimovo should be required under PREA. This would be used to bridge to the JRA indication for Naprosyn." Furthermore, all agreed that the "**efficacy of Vimovo tablets for juvenile arthritis and peptic ulcer disease can be extrapolated from the current data available for adults"**
- Listed below are the two PMRs that were decided upon:
    - **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[6]).
        - A safety and population pharmacokinetic (PK) study in adolescents with JRA who are ages 12 years to 16 years 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."
    - **PMR 1634-1:**
        - An analogous study in children ages 2-11 years.
            - Although the current submission is in response to only PMR 1634-2, included below are the details relevant to PMR 1634-1.

The following is taken from the DPARP consult memo by Dr. Sarah Yim (DAARTs 11/25/16):

5 By Division of Arthritis and Analgesic Products (DAAP), DGIEP, PMHS, and PeRC
6 Juvenile rheumatoid arthritis (JRA) is now called juvenile idiopathic arthritis (JIA)

"In October 2011, DGIEP consulted DPARP on the design of the proposed PMR study in 12 to <17 year olds. DPARP agreed that the proposed design of the study appeared adequate to meet the intent of the postmarketing requirement.

In December 2011, DGIEP met with the Sponsor to discuss the Sponsor's requests for modification of the PMR requirement and requested DPARP's input for that meeting.
The Sponsor requested a release from the requirement to study pediatric patients who cannot swallow a solid dosage form, which they estimated to be children <6 years old, because feasibility work on the formulation suggested that it would not be feasible to develop a non-solid dosage form (b) (4) *. In addition, the sponsor provided data from the IMS health database that the number of JIA patients 2 to <6 years old who require ongoing chronic NSAID therapy and are at risk for developing gastric ulcer or ulcer complication is expected to be low. In the IMS health database, the fraction of patients receiving NSAID and PPI prescriptions in the 2 to <6 year old age group was* (b) (4) *% of the total number of patients in this age group who received NSAID prescriptions. DPARP concurred with the Sponsor's request for partial waiver for the 2 to < 6 year old age group. Although DGIEP and DPMH did not concur with the partial waiver request at the meeting, after further internal discussion, a post-meeting note was sent to the Sponsor indicating that a partial waiver would be considered with additional data and justification.*

In June 2012, the Sponsor contacted DGIEP[7] to report that since the initiation of the adolescent study in JIA, they received new feedback from investigators indicating that the new treatment guidelines and practices for JIA would make the Vimovo PREA-required study in 2 to <12 year olds infeasible. In early May 2012, the Sponsor conducted a meeting with key investigators in JIA trials to understand the current treatments and research practices in 2-11 year-olds with JIA. The feedback from this group of specialized researchers in JIA included the following:

1) *There is no unmet need for NSAID associated gastric ulcer risk reduction in JIA patients aged 2-11*
    a. *This is a very rare event (as judged by NSAID associated ulcer complication rate), and mostly children are prescribed a concomitant gastroprotective agents for GI symptoms (e.g. dyspepsia, etc).*
2) *NSAID associated GI symptoms occur in 30-60% of JIA patients aged 2-11*
    a. *Prescribers are comfortable with naproxen and esomeprazole, and familiar with established safety profiles*
    b. *Prescribers readily prescribe/recommend PPI or H2 receptor antagonist as needed for GI symptoms related to NSAID therapy. Vimovo does not have this indication.*
    c. *Monocomponents permit goal of lowest possible dose for shortest period of time by allowing flexible dosing of NSAID and separate dosing and potentially even prn (as needed) PPI or H2 receptor antagonist*
    d. *For patients with history of NSAID associated GI symptoms, prescribers do turn to more selective COX-2 inhibitors such as meloxicam and celecoxib; these selective drugs are often limited by formulary access and are not often used because of this, Vimovo prescribers may have some of these same challenges, or even more hurdles in terms of access.*
3) *Study limitations for JIA patients aged 2-11 include:*
    a. *Study needs limited intervention, almost RWE[8]/Non-interventional/registry to allow for parent and child willingness to participate as study participation does not provide any benefit to them, only burden of participation.*
        i. *Access to monocomponents (different formulation) is straight forward and even OTC, so there is no unmet need medically, or a clear reason to enroll studies in such a trial.*

7 From e-mail of June 5, 2012 from Laura Garcia-Davenport of Astra Zeneca to Stacy Barley of DGIEP
8 RWE not defined by Sponsor; acronym is unclear.

ii. Investigators recommend no blood draws based on their experience with other studies in this age group.

DPARP concurred with the Sponsor's request for a waiver on the grounds that the product did not represent a meaningful therapeutic benefit over the monoproducts and was not likely to be used in a substantial number of patients due to the changing treatment patterns referenced by the Sponsor. DGIEP requested additional data on the prevalence and incidence of gastric ulcers in this age group. The Sponsor responded with their analyses in two independent databases, (b) (4) *to quantify the prevalence and incidence of gastric ulcer (GU) and duodenal ulcer (DU) for children age 2-11 years old with JIA*[9]

(b) (4)

- In August 2013, due to recruitment challenges, Sponsor requested a deferral extension of the due date (October 15, 2013) for the deferred adolescent study (PMR 1634-2) until December 2015. In this request, the Sponsor proposed numerous changes to the study, including the age of the subjects, dosing, sample size and distribution of subjects between groups, and the visit schedule.
- In September 2013, after further internal discussion[10] and additional submissions from the Sponsor (see details in italics above), PMR 1634-1 was ultimately

9 From e-mail of June 29, 2012 from Laura Garcia-Davenport of Astra Zeneca to Stacey Barley of DGIEP

released and a partial waiver was granted in JIA patents ages 2-11 "because reasonable attempts to produce a pediatric formulation for this age group had failed."

- In October 2013, a Deferral Extension was granted for PMR 1634-2.
- In December 2015, the final clinical study report for the adolescent study to fulfill PMR 1634-2 was submitted.
- In June 2016, the current efficacy supplement was submitted; this efficacy supplement also includes the potential fulfillment of PREA PMR 1634-2..
- In February 2017, although, the Sponsor did not propose an indication originally[11], after internal discussion with DGIEP, DPMH, DPARP and PERC (meeting February 15, 2017) and concurrence with Sponsor, a decision was made to expand this indication to include pediatric JIA patients ages 12-17. Provided final determination by the Clinical Pharmacology and Pharmacometrics Reviewers that the applicant's exposure matching approach is adequate (the final determination s pending at the time of this Review).
    - It was agreed that despite the change in management of JIA patients (to include more DMARDs as first line therapy (as opposed to NSAIDs)[12] there would still exist a population who would benefit from use of Vimovo. This decision was supported by a recent review by Office of Surveillance and Epidemiology (OSE)[13] and a recent response (to IR) from the Sponsor[14]. However, both reviews acknowledge the limitations of the data available (including the retrospective record reviews of 344 patients). See relevant conclusions from each below.

- ***Sponsor Response to IR***

- *From retrospective record reviews of 344 patients*[15]

Table 1 Incidence of Gastroduodenal Injury

Event	No NSAID	NSAID	NNH[2]
Abdominal Pain	33 (14.6%) n=226	96 (27.9%) n=344	1/(.279-.146) = 8.
GI lesion, Ulcer[1]	1 (7.1%) n=14	14 (29.8%) n=47	1/(.298-.071) = 5

1. GI evaluation was performed in those with significant abdominal pain
2. NNH = Number Needed to Harm; rounded up to the next whole number

- *"Based on this the available information, the authors conclude that "NSAID use in children with arthritis frequently leads to gastroduodenal injury, with*

10 Including PERC meeting on August 21, 2013
11 proposed edits to the label were only for changes to sections 8.4 (pediatric use) and 12.3 (pharmacokinetics) and corresponding sections of highlights
12 Beukelman T et al., "2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features." Arthritis Care & Research, April 2011, 63(4):465-582.
13 By Joel L. Weissfeld, MD on 01/25/2017
14 Dated 1/20/16
15 Dowd JE, Cimaz R, Fink CW. Nonsteroidal Antiinflammatory Drug-Induced Gastroduodenal Injury in Children. Arthritis Rheum 1995; 38:1225-1231.

an estimated incidence and relative risk that are comparable to the rates found in adults with arthritis taking NSAIDs".

- ***OSE: Division of Epidemiology***
  "Serious upper GI complications from NSAIDs seem no more frequent in JIA than normally observed in adults."

2.6 Other Relevant Background Information

See Section 2.5 above

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. All sites were located in the United States the Office of Scientific Investigations (OSI) did not perform any clinical inspections.

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3.2 Compliance with Good Clinical Practices

According to the Sponsor, Study D1120C00037 was conducted in accordance with the principles outlined in the Declaration of Helsinki, the Guidance for Good Clinical Practice (GCP) outlined by the International Conference on Harmonisation (ICH), United States 21 Code of Federal Regulations (CFR) Part 312, and 21 CFR Parts 50 and 56 (concerning informed consent and IRB regulations), as well as local ethical and legal requirements. Specifically, the study was based on adequately performed laboratory and animal experimentation; the study was conducted under a protocol reviewed by an IRB; the study was conducted by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the patients were respected; and each patient gave his/her informed consent before any tests or evaluations were performed.
In addition, an Institutional Review Board (IRB)/Ethics Committee (EC) approved the final study protocol,

3.3 Financial Disclosures

The Sponsor was asked to submit signed copies of forms 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators" to certify that no financial

arrangement with the listed clinical investigators were made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a). These forms were pending at the time of this Review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sponsor has proposed two strengths of Vimovo containing either 375 mg of enteric coated naproxen or 500 mg of enteric coated naproxen surrounded by 20 mg of immediate release esomeprazole magnesium.

4.2 Clinical Microbiology

This section is not applicable for the current application.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted in support of this NDA.

4.4 Clinical Pharmacology

Please see the Clinical Pharmacology Review by Dilara Jappar, PhD for further information and details.

4.4.1 Mechanism of Action

Vimovo consists of an immediate-release esomeprazole magnesium layer and an enteric-coated naproxen core. As a result, esomeprazole is released first in the stomach, prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5.

Naproxen (a NSAID) is a proprionic acid derivative that reduces prostaglandin production and leukocyte activation by inhibiting the cyclooxygenase enzyme pathway.

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity

Vimovo has analgesic, anti-inflammatory, and antipyretic properties contributed by the naproxen component. Naproxen is a potent inhibitor of prostaglandin synthesis in vitro.

Naproxen (a NSAID) is a proprionic acid derivative that reduces prostaglandin production and leukocyte activation by inhibiting the cyclooxygenase enzyme pathway.

4.4.2 Pharmacodynamics

Please see the Clinical Pharmacology and Pharmacometrics Reviews for information and details.

4.4.3 Pharmacokinetics

Please see the Clinical Pharmacology and Pharmacometrics Reviews for information and details.

5 Sources of Clinical Data

5.1 Table of Clinical Studies/Trials

Table 1: Table of Clinical Trial

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Populati
D1120C00037A	PK and Safety	To evaluate the safety and tolerability and PK characteristics of Vimovo in adolescents aged 12 to 16 years, with JIA.	US-only, multicenter, open-label, single arm, non-comparator study design	• Patients with baseline weight <38 kg will receive 250 mg/20 mg tablets BID. • Patients with baseline weight of 38 kg to <50 kg will receive either 250 mg/20 mg BID or 375 mg/20 mg tablets BID. • Patients with baseline weight of 50 kg to <75 kg will receive either 375 mg/20 mg or 500 mg/20 mg tablets BID. • Patients with baseline weight ≥75 kg will receive 500 mg/20 mg BID Oral administration	46 Enrolled 36 Completed	Pts 12-16 with a his JIA, that require d NSAID th

5.2 Review Strategy

In response to PREA PMR 1634-2, The Sponsor submitted Study D1120C00037: A 6 month, multicenter, open-label, safety and population PK study in adolescents ages 12 -16 years with JIA who require treatment with NSAIDs. This medical officer reviewed, in detail, the safety portion of this study in Section 7. In addition, various relevant aspects of study D1120C00037 are outlined below in Section 5.3.
Clinical pharmacology and pharmacometric aspects of the submission were reviewed by their respective reviewers. Furthermore, since the Sponsor included exploratory endpoints (in relation to the treatment of JIA), The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) reviewed these exploratory efficacy endpoints. See DPARP consult by Dr. Sarah Yim (in DARRTs dated 11/25/16) for complete details.

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5.3 Discussion of Individual Studies/Clinical Trials

Study D1120C00037

Some elements of Study D1120C00037 are presented below. See DPARP consult by Dr. Sarah Yim (in DARRTs dated 11/25/16) for further details.

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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 Years, Inclusive, with Juvenile Idiopathic Arthritis (JIA)

Objectives:
Primary Objective: To evaluate the safety and tolerability of Vimovo in adolescents ages 12-16 years, inclusive, with JIA.

Secondary Objective: To evaluate the pharmacokinetic (PK) characteristics of Vimovo in adolescents ages 12 -16 years, inclusive, with JIA.

Exploratory Objective: To evaluate the signs and symptoms of JIA in adolescents ages 12 -16 years, inclusive, receiving Vimovo

Study Population:
Some key inclusion/exclusion criteria are listed below. Of note, patients who had a history of peptic ulcer complications were excluded from this pediatric study. This exclusion criterion is in contrast to it being an inclusion criterion in the pivotal studies of the adult indication. However, after internal discussion and consultation with DPMH, it was agreed that the inclusion of pediatric patients with a history of PUD in a 6 month long trial would be an unacceptable risk[16]. In addition, it had previously been agreed that full extrapolation from adults to pediatrics (for JIA indication) would be acceptable. Thus, acceptable PK and safety data would be sufficient.

Key Inclusion Criteria

- Male and non-pregnant female patients age 12 to 16 years
- Diagnosed with JIA
- For whom it was appropriate (in the Investigator's judgment) to receive up to 6 months of continuous treatment with Vimovo

Key Exclusion Criteria

- Systemic JIA with systemic features within the past 6 months
- Treatment with naproxen within the past 4 weeks

16 Essentially all patients on chronic NSAID therapy are at risk of developing ulcers.

- History of peptic ulcer complications (PUD), acute uveitis, cardiovascular or cerebrovascular disease
- Other medical conditions that might have confounded the study or put the patient at greater risk

Treatments Administered/Selection of Doses

Naproxen dose was determined by the patient's weight at Baseline (see Table 2 below) and investigator's discretion according to published clinical guidelines for naproxen use[17] . The target dose of the naproxen component was to be within the range of 10-20 mg/kg/day divided twice daily (BID) with a maximum daily dose of 1000 mg.

Table 2: Doses Administered

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

17 Cassidy et al 2011

Disposition of Subjects

- 46 patients were enrolled and dispensed study drug
- 36 patients completed 6 months of study drug treatment
- 10 patients discontinued prematurely
  - 4 because of AEs[18]
  - 1 because of severe protocol noncompliance (could not swallow study drug)
  - 2 were lost to follow-up, and
  - 3 withdrew consent

Demographic and Other Baseline Characteristics

Patients were mostly Caucasian and mostly female, similar to the pediatric JIA population in the US. There was a mean age of approximately 14 with an acceptable distribution across the various ages. See Table 3 below for further details of the demographic and other baseline characteristics.

[18] See Section 7 for further details.

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Table 3: Demographic and Other Baseline Characteristics

	Vimovo 250 mg/20mg (N=4)	Vimovo 375 mg/20 mg (N=20)	Vimovo 500 mg/20mg (N=22)	Total (N=
Age (yrs), n(%)				
Mean	12.8	13.6	13.8	13.6
12	2 (50)	7 (35)	4 (18)	13 (28
13	1 (25)	4 (20)	7 (32)	12 (26
14	1 (25)	2 (10)	2 (9)	5 (11)
15		5 (25)	7 (32)	12 (26
16		2 (10)	2 (9)	4 (9)
Gender, n(%)				
Female	3 (75)	15 (75)		33 (72
Male	1 (25)	5 (25)		13 (28
Race, n(%)				
White	4 (100)	15 (75)	17 (77)	36 (78
African-Am.	0	3 (15)	2 (9)	5 (11)
Asian	0	0	2 (9)	2 (4)
Other[1]	0	2 (10)	1 (5)	3 (7)
Weight (kg)				
Mean	39.3	53.8	59.4	55.2
Median	38.5	50.5	58.0	54.5
Min, Max	37, 43	42, 76	49, 76	37, 76

Adapted from Study D1120C00037 CSR

6 Review of Efficacy

Efficacy Summary

Study D1120C00037 was designed as a PK/safety study. The Sponsor included exploratory efficacy analyses wherein the primary outcome was a composite endpoint similar to composites that are typically used in pediatric JIA trials. See DPARP consult by Dr. Sarah Yim (in DARRTs dated 11/25/16) for further details. There were no gastrointestinal efficacy endpoints explored in the study.

6.1 Indication

The Sponsor originally did not seek a pediatric indication for Vimovo tablets; however, after review of the data (and discussion-see Section 2.5 and 5.3) the indication below (edits in red) was proposed by DGIEP. Provided final determination by the Clinical Pharmacology and Pharmacometrics Reviewers that the applicant's exposure matching approach is adequate (the final determination s pending at the time of this Review). At the current time, the exact wording of the pediatric indication is still under negotiation.

VIMOVO is a combination product that contains naproxen and esomeprazole magnesium. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults; and in pediatric patients 12 years of age and older with juvenile idiopathic arthritis (JIA) to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers

6.1.1 Methods

See DPARP consult memo by Dr. Sarah Yim for further details.

6.1.2 Demographics

See Section 5.3 above.

6.1.3 Subject Disposition

See Section 5.3 above and DPARP consult by Dr. Sarah Yim for further details.

6.1.4 Analysis of Primary Endpoint(s)

See DPARP consult by Dr. Sarah Yim for details.

6.1.5 Analysis of Secondary Endpoints(s)

See DPARP consult by Dr. Sarah Yim for further details.

6.1.6 Other Endpoints

See DPARP consult by Dr. Sarah Yim for further details.

6.1.7 Subpopulations

See DPARP consult by Dr. Sarah Yim for further details

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Fixed doses of Vimovo containing 250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg naproxen/esomeprazole) were used during Study D1120C00037 Please see the clinical pharmacology/pharmacometrics review for more information. Also see Section 7.2.2 below.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See DPARP consult by Dr. Sarah Yim for further details.

6.1.10 Additional Efficacy Issues/Analyses

See DPARP consult by Dr. Sarah Yim for further details

7 Review of Safety

No unexpected adverse events were seen during Study D1120C00037. Thus, the data from Study D1120C00037 in JIA patients 12 to <17 years of age do not raise new safety concerns and do not warrant new safety-related labeling changes.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

To support the safety of Vimovo in adolescent patients ages 12-16 years, the Sponsor submitted data from Study D1120C00037. 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.

7.1.2 Categorization of Adverse Events

Per the sponsor, all adverse events (AEs) were coded using MedDRA version 17.1 and classified by system organ class (SOC) and preferred term. The appropriateness of the applicant's coding was assessed by comparing the preferred terms to the verbatim terms recorded by investigators within a sampling of case report forms and adverse event dataset. In general the coding appeared to be accurate.
All TEAEs (AEs that occurred on or after the date of first dose of study treatment) were collected from administration of Vimovo (Visit 2, baseline) and throughout the treatment period and follow-up period.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

Safety was assessed from Study D1120C00037. Although the number of patients included in the safety population was small (46 patients), both naproxen and esomeprazole are approved in adolescent patients, thus the safety is also supported by these approvals.

Traditionally, in evaluating NSAID toxicity one would want to pay particular attention to gastrointestinal events[19] and cardiovascular events[20] including elevations in blood pressure. Height, ophthalmologic examination for uveitis, and 12-lead ECG were assessed at Screening. All other safety assessments (adverse events [AEs], SAEs, concomitant medications, physical examinations with vital signs and weight, and clinical laboratory tests) were performed at each scheduled visit to the study site; and in addition, AEs, SAEs, and concomitant medications were assessed during the scheduled

19 Patients with prior history of peptic ulcer complications were excluded from the study. See section 5.3
20 In an adolescent patient population, potential cardiovascular events would be much less common than in an adult patient population. However, Patient with cardiovascular or cerebrovascular disease, based on history or risk factors were excluded from the study.

telephone calls. Urine pregnancy tests were performed at baseline, Month 3, and Month 6.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 4 below provides the number of individual study participants exposed to each treatment dose in Study D1120C00037. As summarized below, the mean duration of exposure was 165 days, with a range from 8 to 218 days.

Table 4: Duration of Exposure to Study Drug (Safety Analysis Set)

	Vimovo 250 mg/20mg (N=4)	Vimovo 375 mg/20 mg (N=20)	Vimovo 500 mg/20mg (N=22)	Total (N=46)
Duration of exposure (days)				
Mean (SD)	154 (48)	168 (37)	165 (41)	165 (39)

Adapted from Table 12-1 of Study D1120C00037 CSR

As shown in Table 4, three Vimovo strengths were used in this study: 250 mg/20 mg, 375 mg/20 mg, and 500 mg/20 mg where 250 mg, 375 mg, and 500 mg represent the naproxen strength of the tablets and the esomeprazole magnesium strength was 20 mg for all tablets. The VIMOVO strength for each patient was determined by the patient's weight at baseline and "based on Investigator's discretion according to published clinical guidelines for naproxen use". The target dose of the naproxen component was within the range of 10-20 mg/kg/day divided BID with a maximum daily dose of 1000 mg

Table 5: Study Treatment Dose

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

7.2.2 Explorations for Dose Response

The Clinical Pharmacology/Pharmacometrics reviews were not available at the time of writing this Clinical Review; please see the Clinical Pharmacology/Pharmacometrics review for details on the explorations of dose response.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Safety was assessed by height, ophthalmologic examination for uveitis, and 12-lead ECG at Screening; concomitant medications and AE monitoring at each visit and scheduled telephone call; urine pregnancy test (female patients); and change from baseline in physical examinations with vital signs (BP, oral temperature, pulse rate, weight) and clinical laboratory tests at each visit. See Table 6 below for detailed information. Overall the safety testing for the pediatric clinical program appeared adequate to assess the primary safety concerns associated with NSAIDs and PPIs.

Table 6: Schedule of Assessments

	Screening period	Open-label treatment period							2-week follow-up period
Visit	1[1]	2[1]	3	4 (TC)[2]	5	6 (TC)[2]	7 (TC)	8/ET[3]	9[2] (TC)[4]
Study day	-30 to -1	1	23-37	53-67	83-97	113-127	143-157	173-187	187-201
Month	-1	0	1	2	3	4	5	6	6.5
Signed Informed Consent/Assent	X								
Medical & Surgical History	X								
Review of JIA history	X								
Inclusion/exclusion criteria	X	X							
Urine pregnancy (dipstick) test (females)	X	X			X			X	
Demography	X								
Weight (kg) and height (cm)	X	X[5]	X[5]		X[5]			X[5]	
Physical examination	X	X	X		X			X	
Vital signs (BP, pulse rate, oral temperature)[6]	X	X	X		X			X	
12-lead ECG[7]	X								
Ophthalmologic examination for uveitis[8]	X								
Clinical chemistry & hematology[9]	X	X	X		X			X	
Urinalysis[9]	X		X		X			X	
PK blood sample collection[10]			X		X				
Scheduled telephone call				X		X	X		X

continued

	Screening period	Open-label treatment period							2-week follow-up period
Visit	1[1]	2[1]	3	4 (TC)[2]	5	6 (TC)[2]	7 (TC)	8/ET[3]	9[2] (TC)[4]
Study day	-30 to -1	1	23-37	53-67	83-97	113-127	143-157	173-187	187-201
Month	-1	0	1	2	3	4	5	6	6.5
ACR Pediatric Response (JIA activity):									
Physician's global assessment of disease activity		X	X		X			X	
Parent's global assessment of overall well-being		X	X		X			X	
CHAQ		X	X		X			X	
Number of joints with active arthritis		X	X		X			X	
Number of joints with limited range of motion		X	X		X			X	
Serum CRP concentration or ESR[11] (markers of acute inflammation)		X	X		X			X	
Study drug dispensing[12]		X	X		X				
Collect study drug			X		X			X	
AE recording[13]			X	X	X	X	X	X	X
SAE recording[14]		X	X	X	X	X	X	X	X
Medications, prior & concomitant[15]	X	X	X	X	X	X	X	X	X

ACR = American College of Rheumatology; AE = adverse events; BP = blood pressure; cm = centimeter; CHAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; ECG = electrocardiogram; eCRF = electronic case report form; ESR = erythrocyte sedimentation rate; ET = Early Termination; JIA = juvenile idiopathic arthritis; kg = kilogram; PK = pharmacokinetics; SAE = serious adverse event; TC = telephone call

[1] Visits 1 (Screening) and 2 (baseline) could have been combined if results from all assessments at Visit 1 were obtained at the time of Visit 1. If Visits 1 and 2 were conducted on the same day, visit procedures that were specific to Visit 2 as outlined in the table had to be conducted during Visit 1, e.g., conducting the ACR Pediatric Response assessments and collecting SAEs.

[2] Scheduled telephone calls occurred at Months 2, 4, and 5 and at 2 weeks following treatment (Month 6.5).
[3] Patients who discontinued early from the study must have undergone all assessments and evaluations indicated for Visit 8. Patients who discontinued prior to Visit 5 provided a PK sample and the time of the last dose was recorded. If the PK sample was not collected for these patients, this was not considered a deviation from the protocol.
[4] The telephone call during the 2-week safety follow-up period was required for all patients (i.e., patients who completed the full 6 months of treatment, patients who completed less than 6 months of treatment, patients who discontinued early from the study, and patients who took at least 1 dose of study drug).
[5] Only weight (kg) was measured.
[6] Vital signs measurements were performed predose after at least 10 minutes in the supine position. Age and size-appropriate BP cuffs were used for BP measurements.
[7] ECG was conducted locally and read/interpreted by the Investigator.
[8] The ophthalmologic examination for uveitis was not required if the patient had had a recent examination prior to the Screening visit and the examination fell within the timeframe as described in Table 9-3. If the patient's last examination was outside of the recommended guidelines in relation to the Screening visit, the examination had to be completed. Documentation of the previous examination conducted prior to Screening had to be provided and reviewed by the Investigator.
[9] If Visit 2 occurred greater than 7 days after Visit 1, clinical chemistry, hematology, and urinalysis had to be repeated to ensure eligibility. A urine pregnancy test for all females also had to be repeated at this time. If Visit 2 occurred 7 days or less after Visit 1, any laboratory values obtained at Visit 1 did not need to be repeated.
[10] On PK sampling days, the precise time of medication intake and blood draws was recorded:
Sparse sampling (Months 1 and 3): Sparse PK samples were obtained between 0.5 and 1 hour postdose or between 2 and 3 hours postdose. For sampling between 0.5-1 hour, the study drug was taken at the study center and a study nurse noted the exact time of dose intake and sampling in the eCRF. For sampling between 2-3 hours, patients took the dose at the study center or called the study center at the exact time of dose intake to allow for accurate recording of the time of dosing and the time of sampling in the eCRF
Frequent sampling (Month 1 only): Patients contributing frequent PK samples took their study drug at the study center. Frequent PK samples were obtained predose and at 0.5, 1, 1.5, and 3 hours (±5 minutes) postdose on Month 1.
[11] Either serum CRP or ESR as a marker of acute inflammation was completed. If the patient had a CRP test performed at the baseline visit, then the CRP was obtained at the remaining visits. If the patient had an ESR performed at the baseline visit, then the ESR data was obtained at the remaining visits.
[12] Study drug was dispensed at Visit 1 if Visits 1 and 2 procedures had been conducted on the same day and the patient had been deemed eligible to participate in the study.
[13] AEs were collected from administration of VIMOVO until the end of the study, including follow-up.
[14] SAEs were collected from the time when informed consent/assent was signed (Visit 1, Screening) until the end of the study, including follow-up.
[15] Other medications, including over-the-counter medications and non-prescription dietary supplements that were considered necessary for the patient's safety and well-being, were given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.
Note: Confirmatory serum pregnancy tests were performed on all females who had a positive urine (dipstick) pregnancy test. Females with a positive urine (dipstick) pregnancy test and a negative serum pregnancy test could be enrolled or could continue in the study.
Note: For urinalysis, an initial dipstick was performed and if abnormal, a sample was sent to the laboratory for a complete urine analysis.
Note: Clinical laboratory tests were repeated at the Investigator's discretion if the results were not within the normal clinical reference range. Results from any repeated laboratory tests were reviewed by the Investigator and the patient's eligibility for the study confirmed prior to the patient being dispensed study drug.

CSR Study D1120C00037 Table 9-2 pg 34-35

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4 above and the Clinical Pharmacology/Pharmacometrics reviews.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events associated with the use of NSAIDs and PPIs have been studied and reported extensively in the literature. The labeling of all NSAID products includes a Medication Guide and a Boxed Warning highlighting the potential for increased risk of cardiovascular events and the serious potentially life-threatening gastrointestinal bleeding associated with their use. There were no cardiovascular adverse events or gastrointestinal bleeding adverse events observed during this study.

7.3 Major Safety Results

An overview of the safety results in the study is summarized in Table 7 below. Consistent with historical JIA trials, the majority (80%) of patients experienced an

adverse event[21]. Each row will be discussed in the sections following. For the second row, Treatment-Emergent Adverse Events which occurred in two or more patients will be presented.

Table 7: Safety Overview of Treatment-Emergent Adverse Events (TEAEs)

	Vimovo 250 mg/20mg (N=4)	Vimovo 375 mg/20 mg (N=20)	Vimovo 500 mg/20mg (N=22)	Total (N=46)
Deaths, n (%)	0	0	0	0
Serious Adverse Events (SAEs)				
# of events	0	1	0	1
Patients with SAE, n (%)	0	1 (5)	0	1 (2)
TEAEs				
# of events	14	39	59	112
Patients with TEAE, n (%)	4 (100)	16 (80)	17 (77)	37 (80)
TEAEs leading to Discontinuation				
# of events	1	1	3	5
Patientts with DAE, n (%)	1 (25)	1 (5)	2 (9)	4 (9)

Adapted from Table 12-2 of Study D1120C00037 CSR

7.3.1 Deaths

There were no deaths reported during the study.

7.3.2 Nonfatal Serious Adverse Events

There was only one serious nonfatal adverse event (SAE) which occurred in one patient.

This single SAE (acute hepatitis) occurred in a 13-year old female with a past medical history significant for hepatic steatosis on prior liver biopsy. On Day 22 of study drug treatment, the patient experienced increased serum levels of AST and ALT (213 and 169 U/L, respectively) compared to baseline (ALT =45 U/L and AST =56 U/L). Values continued to increase, to a maximum of 1478 and 1912 U/L, respectively. The patient had signs and symptoms c/w hepatitis; serologic testing was non-reactive for hepatitis A, B, and C. The study drug was permanently discontinued on Day 88. The patient was hospitalized for a liver biopsy, which showed mixed inflammatory changes. A

21 According to Sarah Yim, M.D. Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

diagnosis of acute hepatitis with a possible etiology of drug induced hepatitis or biliary cirrhosis was given. Patient was treated accordingly. By Day 157, the patient recovered and both events (acute hepatitis, increased LFTs) were considered resolved.

It is unclear in Vimovo was the cause of these adverse events, but hepatoxicity is a known side effect of Vimovo use and NSAID use in general.

7.3.3 Dropouts and/or Discontinuations

These were three other patients who discontinued the study secondary to four TEAEs. See Table 8 below.

Table 8: Dropouts and/or Discontinuations

Age/sex	Vimovo Dose	TEAE	Description	Medical Reviewer's Assessment
12 y.o. Female	250 mg/20 mg	Hypoaesthesia	Patient was discontinued due to one day of numbness of the palate area which began on Day 80 and lasted one day. The patient was treated with Benadryl and discontinued from study drug.	Numbness of the palate area was a transient, nonspecific symptom that did not appear to be clearly associated with study drug treatment. This does not appear to represent a new safety signal.
13 y.o Male	500 mg/20 mg	Abdominal pain upper Dyspepsia	Patient was discontinued due to upper abdominal pain and dyspepsia. Study drug was permanently discontinued after 8 days of treatment and symptoms resolved without treatment a few days later. This patient had additional AEs of vomiting and diarrhea.	This patient experienced well-known and temporally-associated symptoms associated with NSAID treatment, which are already described in the current Vimovo label.
15 yo Female	500 mg/20 mg	Worsening JIA	Patient was discontinued due to worsening of her JIA which began on Day 108 of treatment. Study drug was permanently discontinued on Day 115 of study drug treatment and she was switched to treatment with diclofenac sodium and prednisone.	This patient experienced worsening of JIA, which is likely due to the natural history of her disease. Progression of disease would not be unexpected given that NSAIDs do not provide disease-modifying effects for JIA.

Adapted from CSR D1120C00037 pgs 108-109

In summary, the above discontinuations do not raise new safety concerns and do not demonstrate a need for safety labeling changes.

7.3.4 Significant Adverse Events

All significant adverse events are described in respective sections.

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7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An overview of the safety in the study is summarized in Table 9 below.

As would be expected for an NSAID and a PPI, the most common adverse events were in the Gastrointestinal (GI) Disorders System-Organ-Class (SOC), with approximately 40% of all patients experiencing a GI AE. The most common preferred terms in this SOC included upper abdominal pain, diarrhea, nausea, abdominal discomfort, dyspepsia, and vomiting.

The second most common SOC was Infections and Infestations. Typically, NSAIDs and PPIs usage would not be expected to increase the risk for infections. However, infections may occur more frequently in JIA patients, in part due to the underlying immune disorder and in part due to immunosuppressive agents used to treat the disorder. The reported infections were consistent with those commonly seen in these patients, such as upper respiratory tract infections, sinusitis, and viral gastroenteritis. In addition, these infections are also typical infections one might observe in a general pediatric population. The most common SOC and preferred terms reported in this pediatric study appear be consistent with the previous adult studies for Vimovo. No new safety signals were evident; therefore, no safety labeling changes are warranted on the basis of this submission.

Table 9: Treatment-Emergent Adverse Events (TEAE) Occurring in at Least 2 Patients Total, by MedDRA System-Organ-Class (SOC) and Preferred Term (PT)

	Vimovo 250 mg/20mg (N=4)	Vimovo 375 mg/20 mg (N=20)	Vimovo 500 mg/20mg (N=22)	Total (N=46)
Pts with any TEAE, n (%)	4 (100)	16 (80)	17 (77)	37 (80)
Gastrointestinal Disorders, n (%)	1 (25)	8 (40)	8 (36)	17 (37)
Abdominal pain upper	0	3 (15)	2 (9)	5 (11)
Diarrhea	0	2 (10)	2 (9)	4 (9)
Nausea	0	3 (15)	1 (5)	4 (9)
Abdominal discomfort	0	2 (10)	0	2 (4)
Dyspepsia	0	0	2 (9)	2 (4)
Vomiting	0	1 (5)	1 (5)	2 (4)
Infections/Infestations, n (%)	2 (50)	4 (20)	9 (41)	15 (33)
Upper respiratory tract inf.	1 (25)	2 (10)	6 (27)	9 (20)
Sinusitis	0	1 (5)	4 (18)	5 (11)
Gastroenteritis viral	0	0	2 (9)	2 (4)
Tooth infection	0	1 (5)	1 (5)	2 (4)
Musculoskeletal/connective tis.	2 (50)	2 (10)	2 (9)	6 (13)
Back pain	1 (25)	1 (5)	0	2 (4)
Pain in extremity	0	1 (5)	1 (5)	2 (4)
Injury, poisoning, procedural	0	2 (10)	3 (14)	5 (11)
Ligament sprain	0	0	3 (14)	3 (7)
Nervous system disorders	2 (50)	1 (5)	2 (9)	5 (11)
Headache	1 (25)	1 (5)	2 (9)	4 (9)
General disorders/admin site	0	0	2 (9)	2 (4)
Fatigue	0	0	2 (9)	2 (4)
Immune system disorders	0	1 (5)	1 (5)	2 (4)
Hypersensitivity	0	1 (5)	1 (5)	2 (4)
Neoplasms, benign, malig., unsp	1 (25)	1 (5)	0	2 (4)
Skin papilloma	1 (25)	1 (5)	0	2 (4)
Respiratory, thoracic, mediastin.	0	1 (5)	1 (5)	2 (4)
Cough	0	1 (5)	1 (5)	2 (4)

Source: Table 12-3 of Study D1120C00037 CSR.

7.4.2 Laboratory Findings

In general, there was very little change in laboratory parameters over the course of the study and not of sufficient magnitude to be clinically meaningful. This was corroborated by shift tables, which did not support any consistent trends in laboratory abnormalities over the course of the study (data not shown, Tables 14.3.4.2, 14.3.4.4 CSR).
There were two patients who had changes in laboratory parameters that were notable. As discussed in Section 7.3, the patient with the SAE of acute hepatitis had elevated LFTs, which were considered clinically significant. A second patient who had a normal eosinophil level at Baseline (0.2%) developed an eosinophilia (recorded as a TEAE) at Month1 (7.8%) which persisted at Month 6 (7.4%). However, there was no apparent

clinical correlation with this lab abnormality and no other patient had a TEAE of eosinophilia.

7.4.3 Vital Signs

Vital signs (BP, oral temperature, pulse rate, weight) were collected at each study visit. Mean changes from baseline were generally small. Clinically significant changes in vital signs were recorded as TEAEs. One patient (500 mg/20 mg group) had a TEAE of weight decreased. At baseline, the patient's weight was 60 kg, and height was 171 cm. The patient had a decrease of 3 kg body weight during the Treatment period. Although a 6 pound weight loss may be clinically significant for a particular pediatric patient, there were no other TEAEs of "weight loss". There did not appear to be a trend of weight loss for Vimovo during the study treatment period.

7.4.4 Electrocardiograms (ECGs)

In this pediatric study, all 46 enrolled patients had ECGs performed at Screening. The interpretation of thirty-eight were normal, two were considered borderline and six were read as having clinically insignificant changes. No follow-up ECGs were indicated in this adolescent population with unremarkable baseline ECGs

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies performed.

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of Vimovo was included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Patients received three different doses of Vimovo (250 mg/20 mg; 375mg/20mg; 500mg/20 mg) so adverse event data from each of these doses was compared. There were no obvious AE trends observed. However, given the small study population and thus small number of patients in each dose group,[22] it is difficult to draw any definitive conclusions from this data.

22 Four patients, 20 patients and 22 patients for 250 mg/20 mg; 375mg/20mg and 500mg/20 mg respectively. Different doses of naproxen for each dose group but equivalent amounts of esomeprazole at 20 mg.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were explored.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were explored.

7.5.5 Drug-Drug Interactions

Current labeling for Vimovo reports multiple drug interactions. These include:
drugs that interfere with hemostasis, drugs dependent on gastric pH for absorption (e.g., iron salts, erlotinib, mycophenoloate mofetil, ketoconazole), CYP2C19 or CYP3A4 Inducers, CYP2C19 or CYP3A4 Inhibitors, aspirin, ACE Inhibitors, angiotensin receptor blockers, and beta-blockers, diuretics, antiretrovirals; cilostazol digoxin lithium, methotrexate, cyclosporine, tacrolimus NSAIDs and salicylates, pemetrexed and diazepam,

(b) (4) Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional carcinogenicity data was submitted.

7.6.2 Human Reproduction and Pregnancy Data

The prior labeling for Nexium categorized the drug Pregnancy Category B and prior labeling for Naproxen categorized the drug Pregnancy Category C. In general, the way that data is reflected in the Human Reproduction and Pregnancy Data part of the label has been updated. Thus, this section of the Vimovo label is being revised. The latest draft of this section[23] is below:

Risk Summary
Use of NSAIDs, including VIMOVO, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIMOVO, in pregnant women starting at 30 weeks of gestation (third trimester). There are no adequate and well-controlled studies of VIMOVO in pregnant women.

[23] Label negotiations are ongoing at the time of this review.

VIMOVO contains naproxen and esomeprazole magnesium. Esomeprazole is the S- isomer of omeprazole.

Naproxen
Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, naproxen administered during organogenesis to rats and rabbits at doses less than the maximum recommended human daily dose of 1500 mg/day showed no evidence of harm to the fetus [see Data (b) (4)]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen resulted in increased pre- and post-implantation loss.

Esomeprazole
There are no human data for esomeprazole. However, available epidemiologic data for omeprazole (esomeprazole is the S-isomer of omeprazole) fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use [see Data (b) (4)]. In animal studies with administration of oral esomeprazole magnesium in rats changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole (b) (4)

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Labor or Delivery
There are no studies on the effects of VIMOVO during labor or delivery. In animal studies, NSAIDs, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data
Human Data

Naproxen
When used to delay preterm labor, inhibitors of prostaglandin synthesis, including NSAIDs such naproxen, may increase the risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants.

Esomeprazole
Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2 receptor antagonists or other controls.

A population based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995-99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996-2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837, 317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H2 blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester.

The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data
There are no reproduction studies in animals with VIMOVO, a combination of naproxen and esomeprazole.

Naproxen
Reproduction studies with naproxen administered during the period of organogenesis have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison) rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.56 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of harm to the fetus due to the drug.

Esomeprazole
No effects on embryo-fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) or in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis) administered during organogenesis and have revealed no evidence of harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development were performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times a daily human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg /kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times a daily human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times the daily human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg /kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.2 Lactation
Risk Summary
Limited data from published literature report that naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Esomeprazole is the S-isomer of omeprazole and limited data from published literature suggest omeprazole may be present in human milk. There is no information on the effects of naproxen or omeprazole on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need

for VIMOVO and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Infertility
Females
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including VIMOVO, may delay or prevent rupture of ovarian follicles that may lead to reversible infertility in some women. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Published animal studies have shown that administration of prostaglandin synthesis inhibitors have the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Consider withdrawal of NSAIDs, including VIMOVO, in women who have difficulties conceiving or who are undergoing investigation of infertility.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of effects on growth were included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Proton-pump inhibitor therapy in healthy volunteers may induce acid-related symptoms after withdrawal. This phenomenon called rebound acid hypersecretion was demonstrated after 8 weeks of treatment with a proton-pump inhibitor. If rebound acid hypersecretion does cause acid-related symptoms, there is a potential for PPI dependency.[24]

From the current label:
There is no clinical data on overdosage with VIMOVO.

Overdosage of naproxen:
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred but were rare [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)].

A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD50 of the drug is 500 mg/kg in rats, 1200 mg/kg in mice, 4000 mg/kg in hamsters and greater than 1000 mg/kg in dogs. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Overdosage of esomeprazole:

[24] Waldum, HL, Ovigstad G, Fossmark, R, Kleve PM, Scandvik AK. (2010) "Rebound acid hypersecretion from a physiologic, pathophysiological and clinical viewpoint" *Scandinavian Journal of Gastroenterology* 45 (4):389-394.

A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.
The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - Adverse Reactions). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

8 Postmarketing Experience

Information regarding the quantity of Vimovo product distributed in the US during the last annual reporting period is listed below in Table 10.

Table 10: Distribution Data for Vimovo May 1, 2015 to 30 April 30, 2016

Packaging Configuration	NDC Number	Use	Quantity of Packaged Units Distributed
500 mg/20 mg 60-count Bottle	75987-030-04	Commercial - US	(b) (4) bottles (b) (4) tablets) distributed (1)
375 mg/20 mg 60-count Bottle	75987-031-04	Commercial - US	(b) (4) bottles (b) (4) tablets) distributed (2)
500 mg/20 mg 6-count Bottle	75987-030-73	Commercial - US	(b) (4) bottles (b) (4) tablets) distributed

Table 11 and 12 below list the Serious Expected Events from Serious Unexpected Cases and Serious Unexpected Adverse Events respectively. As may be expected for a NSAID/PPI combination, GI disorders have the most events. This is followed by Musculoskeletal and Connective Tissue Disorders (including events of cervical fracture and ligament sprain which are questionably coded under Injury, Poisoning and Procedural Complications) Review of these events does not indicate any new safety signals.

Table 11: Summary of Serious Adverse Event Reports for Vimovo Delayed Release Tablets Vimovo May 1, 2015 to 30 April 30, 2016

MedRA System Organ Class/Preferred Term	No.
Blood and lymphatic system disorders	**1**
Leukopenia	1
Cardiac disorders	**3**
Myocardial infarction	1
Myocarditis	2
Eye disorders	**5**
Occular hyperaemia	1
Papilloedema	1
Retinal vein thrombosis	2
Vision blurred	1
Gastrointestinal disorders	**15**
Abdominal discomfort	1
Abdominal pain	1
Abdominal pain upper	1
Diarrhoea	1
Diarrhoea haemorrhagic	1
Gastritis	1
Gastrointestinal haemorrhage	3
Gastrointestinal ulcer	1
Gastrooesophageal reflux disease	1
Haematochezia	2
Pancreatitis necrotising	2
General disorders and administration site conditions	**6**
Chest pain	1
Drug interaction	2
Fatigue	1
Injection site haemorrahage	1
Ulcer haemorrhage	1
Hepatobiliary disorders	**2**
Portal vein thrombosis	2
Infections and infestations	**6**
Anaphylactic reaction	1
Diverticulitis	3
Fungal infection	1
Immune system disorders	1
Staphylococcal sepsis	2
Injury, poisoning and procedural complications	**11**
Cervical vertebral fracture	2
Extradural haematoma	2
Fall	4
Ligament sprain	1

Meniscus injury	1
Patella fracture	1
Investigations	**2**
Weight decreased	1
Blood glucose increased	1
Musculoskeletal and connective tissue disorders	**7**
Arthralgia	2
Back pain	2
Joint swelling	2
Rheumatoid arthritis	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps	**2**
Breast cancer female	1
Lymphoma	1
Nervous system disorders	**1**
Dizziness	1
Psychiatric disorders	**1**
Nightmare	1
Renal and urinary disorders	**2**
Acute kidney injury	2
Reproductive system and breast disorders	**1**
Breast mass	1
Respiratory, thoracic and mediastinal disorders	**4**
Asthmatic crisis	1
Dysphonia	1
Dyspnoea	1
Respiratory failure	1
Skin and subcutaneous tissue disorders	**2**
Drug reaction with eosinophilia and systemic symptoms	1
Rash	1
Vascular disorders	**5**
Deep vein thrombosis	2
Haemorrhage	1
Hypertension	1
Peripheral arterial occlusive disease	1
Total	**77**
#of patient cases	28

Table 12: Summary of Serious Unexpected Adverse Event Reports for Vimovo Delayed Release Tablets May 1, 2015 to 30 April 30, 2016

MedDRA System Organ Class/Preferred Term	No.
Cardiac Disorders	**1**
Myocarditis	1
Eye disorders	**1**
Retinal vein thrombosis	1
General Disorders and administrative site conditions	**1**
Drug interaction	1
Hepatobiliary disorders	**1**
Portal vein thrombosis	1
Infections and infestations	**3**
Diverticulitis	2
Fungal infection	1
Injury, poisoning and procedural complications	**3**
Extradural haematoma	1
Meniscus injury	1
Patella fracture	1
Investigations	**1**
Blood glucose increased	1
Musculoskeletal and connective tissue disorders	**1**
Rheumatoid arthritis	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1**
Lymphoma	1
Reproductive system and breast disorders	**1**
Breast mass	1
Respiratory, thoracic and mediastinal disorders	**2**
Dysphonia	1
Respiratory failures	1
Skin and subcutaneous tissue disorder	**1**
Drug reaction with eosinophilia and systematic symptoms	1
Resuscitation	1
Vascular disorders	**1**
Deep vein thrombosis	1
Total	**19**
# of patient cases	15

9 Appendices

9.1 Literature Review/References

See footnotes as necessary.

9.2 Labeling Recommendations

At this time, this medical reviewer is able to propose label recommendations for the Section 1 and Section 8.4 (see below). Currently, clinical pharmacology's proposed recommendations for the DOSAGE AND ADMINISTRATION section (Section 2) and the Pharmacokinetics section (Section 12.3) are still pending. In addition, please note labeling is currently being negotiated with the Sponsor

1 INDICATIONS AND USAGE

(b) (4)

8.4 Pediatric Use

(b) (4)

9.3 Advisory Committee Meeting

There was no advisory committee meeting convened for this sNDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARJORIE F DANNIS
03/01/2017

ANIL K RAJPAL
03/01/2017