CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204592Orig1s002

Trade Name: ZORVOLEX

Generic or Proper Name: diclofenac

Sponsor: Iroko Pharmaceuticals LLC

Approval Date: 08/22/2014

Indication: ZORVOLEX is an NSAID indicated for management of mild to moderate acute pain and osteoarthritis pain.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592/S-002
NDA 204592/S-004

SUPPLEMENT APPROVAL

Iroko Pharmaceuticals LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Paul M. Kirsch
VP, Regulatory Affairs & Quality

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 31, 2014, (S-002) and April 25, 2014, (S-004) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zorvolex (diclofenac) capsules, 18 mg and 35 mg.

We acknowledge receipt of your amendments for S-002, dated December 27, 2013, and January 29 and 31, and February 6, 2014.

Reference is also made to your email dated August 21, 2014, which included the final agreed-upon labeling.

These "Prior Approval" supplemental new drug applications propose the following:

S-002: Addition of a new indication for the management of osteoarthritis pain.

S-004: Changes to the medication guide, in response to our supplement request letter dated April 10, 2014.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Swati Patwardhan
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3170
10903 New Hampshire Avenue
Silver Spring, MD
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable due to the extremely limited incidence of osteoarthritis in the pediatric population.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SHARON H HERTZ
08/22/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZORVOLEX® safely and effectively. See full prescribing information for ZORVOLEX.

ZORVOLEX (diclofenac) capsules, for oral use
Initial U.S. Approval: 1988

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

Cardiovascular Risk

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)**
- **ZORVOLEX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4)**

Gastrointestinal Risk

- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)**

RECENT MAJOR CHANGES

- Indications and Usage, Osteoarthritis Pain (1 2) 8/2014

INDICATIONS AND USAGE

ZORVOLEX is an NSAID indicated for management of mild to moderate acute pain and osteoarthritis pain. (1)

DOSAGE AND ADMINISTRATION

- The dosage for acute pain is 18 mg or 35 mg orally three times a day. (1.2)
- The dosage for osteoarthritis pain is 35 mg orally three times a day. (1.2)
- Use lowest effective dosage for shortest duration consistent with individual patient treatment goals. (1.2)
- ZORVOLEX capsules are not interchangeable with other formulations of oral diclofenac even if the milligram strength is the same. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 18 mg or 35 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac or any components of the drug product. (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
- Perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease or risk factors for CV disease may be at greater risk. Use the lowest effective dose for the shortest duration possible. (5.1)
- Serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation, which can be fatal. Prescribe ZORVOLEX with caution in patients with a prior history of ulcer disease or GI bleeding. Use the lowest effective dose for the shortest duration possible. (5.2)
- Elevation of one or more liver tests and severe hepatic reactions. Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with ZORVOLEX. Discontinue ZORVOLEX immediately if abnormal liver tests persist or worsen. (5.3)
- New onset or worsening of hypertension. Monitor blood pressure closely during treatment with ZORVOLEX. (5.4)
- Fluid retention and edema. Use ZORVOLEX with caution in patients with fluid retention or heart failure. (5.5)
- Renal papillary necrosis and other renal injury with long-term use. Use ZORVOLEX with caution in patients at greatest risk of this reaction, including the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and ACE inhibitors. (5.6)
- Anaphylactoid reactions in patients with the aspirin triad or in patients without prior exposure to ZORVOLEX. Discontinue immediately if an anaphylactoid reaction occurs. (5.7)
- Serious skin adverse events such as exfoliative dermatitis, Stevens - Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Discontinue ZORVOLEX if rash or other signs of local skin reaction occur. (5.8)

ADVERSE REACTIONS

Most common adverse reactions in controlled clinical trials (incidence ≥2% in ZORVOLEX 18 mg or 35 mg group) include, edema, nausea, headache, dizziness, vomiting, constipation, pruritus, diarrhea, flatulence, pain in extremity, abdominal pain, sinusitis, alanine aminotransferase increased, blood creatinine increased, hypertension, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Iroko Pharmaceuticals, LLC at 1-877-757-0676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of ZORVOLEX and aspirin is not generally recommended because of the potential of increased adverse effects including increased GI bleeding. (7.1)
- Concomitant use of ZORVOLEX and anticoagulants have a risk of serious GI bleeding higher than users of either drug alone. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Starting at 30 weeks gestation, ZORVOLEX should be avoided as premature closure of the ductus arteriosus in the fetus may occur. (5.9, 8.1)
- Nursing Mothers: Based on available data, diclofenac may be present in human milk. Exercise caution when ZORVOLEX is administered to a nursing woman. (8.3)
- Hepatic insufficiency: Patients with hepatic disease may require reduced doses of ZORVOLEX. Start treatment at the lowest dose. Discontinue use if efficacy is not achieved with the lowest dose. (2.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2014

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

- **NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. [*see Warnings and Precautions* (5.1)]**
- **ZORVOLEX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. [*see Contraindications* (4)]**

Gastrointestinal Risk

- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. [*see Warnings and Precautions* (5.2)]**

1 INDICATIONS AND USAGE

1.1 Acute Pain

ZORVOLEX is indicated for management of mild to moderate acute pain.

1.2 Osteoarthritis Pain

ZORVOLEX is indicated for management of osteoarthritis pain.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

The effectiveness of ZORVOLEX when taken with food has not been studied in clinical studies. Taking ZORVOLEX with food may cause a reduction in effectiveness compared to taking ZORVOLEX on an empty stomach [*see Clinical Pharmacology (12.3)*]. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5.1, 5.2)*].

Acute Pain

For management of mild to moderate acute pain, the dosage is 18 mg or 35 mg orally three times daily.

Osteoarthritis Pain

For management of osteoarthritis pain, the dosage is 35 mg orally three times daily.

2.2 Dosage Adjustments in Patients with Hepatic Impairment

Patients with hepatic disease may require reduced doses of ZORVOLEX compared to patients with normal hepatic function [*see Clinical Pharmacology (12.3)*]. As with other diclofenac products, start treatment at the lowest dose. If efficacy is not achieved with the lowest dose, discontinue use.

2.3 Non-Interchangeability with Other Formulations of Diclofenac

ZORVOLEX capsules are not interchangeable with other formulations of oral diclofenac even if the milligram strength is the same. ZORVOLEX capsules contain diclofenac free acid whereas other diclofenac products contain a salt of diclofenac, i.e., diclofenac potassium or sodium. A 35 mg dose of ZORVOLEX is approximately equal to 37.6 mg of sodium diclofenac or 39.5 mg of potassium diclofenac. Therefore, do not substitute similar dosing strengths of other diclofenac products without taking this into consideration.

3 DOSAGE FORMS AND STRENGTHS

ZORVOLEX (diclofenac) capsules 18 mg - blue body and light green cap (imprinted IP-203 on the body and 18 mg on the cap in white ink).

ZORVOLEX (diclofenac) capsules 35 mg - blue body and green cap (imprinted IP-204 on the body and 35 mg on the cap in white ink).

4 CONTRAINDICATIONS

ZORVOLEX is contraindicated in patients with:

- known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to diclofenac or any components of the drug product [*see Warnings and Precautions (5.7, 5.8)*].
- a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.13)*].
- perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical studies of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for

CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Inform patients about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Two large, controlled, clinical studies of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [*see Contraindications (4)*].

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as diclofenac, does increase the risk of serious GI events [*see Warnings and Precautions (5.2), Drug Interactions (7.1)*].

5.2 Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including ZORVOLEX, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term NSAID therapy is not without risk.

Prescribe NSAIDs, including ZORVOLEX, with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternative therapies that do not include NSAIDs should be considered.

5.3 Hepatic Effects

Elevations of one or more liver tests may occur during therapy with ZORVOLEX. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (greater than the upper limit of normal [ULN] to 3 times the ULN range) of transaminases have been observed in approximately 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials of diclofenac-containing products, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) were observed in about 2% of approximately 5,700 patients at some time during diclofenac treatment.

In a large, open-label, controlled diclofenac sodium trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (greater than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (greater than 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with ZORVOLEX, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), discontinue ZORVOLEX immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and

"flulike" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with ZORVOLEX, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing ZORVOLEX with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, certain antibiotics, and anti-epileptics).

5.4 Hypertension

NSAIDs, including ZORVOLEX, can lead to new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including ZORVOLEX, with caution in patients with hypertension. Monitor blood pressure (BP) closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use ZORVOLEX with caution in patients with fluid retention or heart failure.

5.6 Renal Effects

Use caution when initiating treatment with ZORVOLEX in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of ZORVOLEX in patients with advanced renal disease. Therefore, treatment with ZORVOLEX is not recommended in patients with advanced renal disease. If ZORVOLEX therapy must be initiated, monitor the patient's renal function closely.

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ZORVOLEX. ZORVOLEX is contraindicated in patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or

without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [*see Contraindications (4)*].

Emergency help should be sought in cases where an anaphylactoid reaction occurs.

5.8 Adverse Skin Reactions

NSAIDs, including ZORVOLEX, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations, and to discontinue ZORVOLEX at the first appearance of skin rash or any other sign of hypersensitivity [*see Contraindications (4)*].

5.9 Fetal Toxicity

Starting at 30 weeks gestation, ZORVOLEX and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (8.1)*].

5.10 Corticosteroid-Responsive Illness

ZORVOLEX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

5.11 Masking of Inflammation and Fever

The pharmacological activity of ZORVOLEX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

5.12 Hematological Effects

Anemia may occur in patients receiving NSAIDs, including ZORVOLEX. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients on long-term therapy with NSAIDs, including ZORVOLEX, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Carefully monitor patients treated with ZORVOLEX who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.13 Use in Patients with Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ZORVOLEX is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma [*see Contraindications (4)*].

5.14 Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. For patients on long-term treatment with NSAIDs, periodically check a CBC and a chemistry profile including liver function tests. Discontinue ZORVOLEX if abnormal liver tests or renal tests persist or worsen.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Gastrointestinal effects [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Hepatic effects [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Congestive heart failure and edema [*see Warnings and Precautions (5.5)*]
- Renal effects [*see Warnings and Precautions (5.6)*]
- Anaphylactoid reactions [*see Warnings and Precautions (5.7)*]
- Serious skin reactions [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Acute Pain

Two-hundred sixteen (216) patients received ZORVOLEX in the completed, 48-hour, double-blind, placebo-controlled, clinical trial of acute pain following bunionectomy. The most frequent adverse reactions in this study are summarized in Table 1.

Table 1 Summary of Adverse Reactions (≥2% in ZORVOLEX 18 mg or 35 mg group) – Phase 3 Study in Patients With Postsurgical Pain

Adverse Reactions	ZORVOLEX 18 mg or 35 mg three times daily* N = 216	Placebo* N = 106
Edema	33%	32%
Nausea	27%	37%
Headache	13%	15%
Dizziness	10%	16%
Vomiting	9%	12%
Constipation	8%	4%
Pruritus	7%	6%
Flatulence	3%	2%
Pain in Extremity	3%	1%
Dyspepsia	2%	1%

*One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as rescue medication for pain management. There was a greater use of concomitant opioid rescue medication in placebo-treated patients than in ZORVOLEX-treated patients. About 82% of patients in the ZORVOLEX 35 mg group, 85% of the patients in the ZORVOLEX 18 mg group, and 97% of patients in the placebo group took rescue medication for pain management during the study.

Adverse Reactions in Patients with Osteoarthritis Pain

Two-hundred two (202) patients received ZORVOLEX in the completed, 12-week, double-blind, placebo-controlled, clinical trial of osteoarthritis pain of the knee or hip. The most frequent adverse reactions in this study are summarized in Table 2.

Table 2 Summary of Adverse Reactions (≥2%) – 12-week Phase 3 Study in Patients With Osteoarthritis Pain*

Adverse Reactions	ZORVOLEX 35 mg N=202	Placebo N=103
Nausea	7%	2%
Diarrhea	6%	3%
Headache	4%	3%
Abdominal Pain Upper	3%	1%
Sinusitis	3%	1%
Vomiting	3%	1%
Alanine Aminotransferase Increased	2%	0
Blood Creatinine Increased	2%	0
Dyspepsia	2%	1%
Flatulence	2%	0

Hypertension	2%	1%

* Adverse reactions that occurred in ≥2% of patients treated with ZORVOLEX and occurred more frequently than in patients treated with placebo

Six-hundred one (601) patients received ZORVOLEX 35 mg either twice or three times daily in a 52-week, open-label, clinical trial in osteoarthritis pain of the knee or hip. Of those, 360 (60%) patients completed the trial. The most frequent adverse reactions in this study are summarized in Table 3.

Table 3 Summary of Adverse Reactions (≥2%) – 52-week Open-label Study in Patients with Osteoarthritis Pain

Adverse Reactions	**ZORVOLEX 35 mg N=601**
Upper respiratory tract infection	8%
Headache	8%
Urinary tract infection	7%
Diarrhea	6%
Nasopharyngitis	6%
Nausea	6%
Constipation	5%
Sinusitis	5%
Osteoarthritis	5%
Cough	4%
Alanine aminotransferase increased	4%
Back pain	3%
Dyspepsia	3%
Procedural pain	3%
Bronchitis	3%
Hypertension	3%
Abdominal pain upper	3%
Influenza	3%
Arthralgia	3%
Contusion	3%
Vomiting	3%
Abdominal discomfort	2%
Aspartate aminotransferase increased	2%
Dizziness	2%
Fall	2%
Abdominal pain	2%

Adverse reactions reported for diclofenac and other NSAIDs:

In patients taking other NSAIDs, the most frequently reported adverse reactions occurring in approximately 1%-10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse reactions reported occasionally include:

Body as a Whole: fever, infection, sepsis
Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope
Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice
Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia
Metabolic and Nutritional: weight changes
Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo
Respiratory System: asthma, dyspnea
Skin and Appendages: alopecia, photosensitivity, sweating increased
Special Senses: blurred vision
Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes, death
Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis
Digestive System: colitis, eructation, fulminant hepatitis with and without jaundice, liver failure, liver necrosis, pancreatitis
Hemic and Lymphatic System: agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia
Metabolic and Nutritional: hyperglycemia
Nervous System: convulsions, coma, hallucinations, meningitis
Respiratory System: respiratory depression, pneumonia
Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria
Special Senses: conjunctivitis, hearing impairment

7 DRUG INTERACTIONS

7.1 Aspirin

When administered with aspirin, the protein binding of ZORVOLEX is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ZORVOLEX and aspirin is not generally recommended because of the potential of increased GI adverse reactions [*see Warnings and Precautions (5.1, 5.2)*].

7.2 Anticoagulants

The effects of anticoagulants, such as warfarin and NSAIDs on GI bleeding, are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that with use of either drug alone [*see Warnings and Precautions (5.2)*].

7.3 ACE-inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors [*see Warnings and Precautions (5.4)*].

This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

7.4 Diuretics

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients [*see Warnings and Precautions (5.4)*]. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ZORVOLEX and these diuretics, observe patients closely for signs of renal failure, as well as to assure diuretic efficacy [*see Warnings and Precautions (5.6)*].

7.5 Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

7.7 Cyclosporine

NSAIDs may affect renal prostaglandins and increase the toxicity of cyclosporine. Therefore, concomitant therapy with NSAIDs may increase cyclosporine's nephrotoxicity. Use caution when NSAIDs are administered concomitantly with cyclosporine.

7.8 Inhibitors or Substrates of Cytochrome P450 2C9 Other Considerations

Diclofenac is metabolized predominantly by cytochrome P450 2C9. Co-administration of diclofenac with another drug known to be metabolized by, or which inhibits, cytochrome P450 2C9 may unpredictably affect the pharmacokinetics of diclofenac or the co-administered drug. Caution should be used to evaluate each patient's medical history when consideration is given to prescribing diclofenac [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation;

Category D starting at 30 weeks gestation.

Risk Summary

There are no adequate and well controlled studies of ZORVOLEX in pregnant women. Starting at 30 weeks gestation, ZORVOLEX, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. ZORVOLEX can cause fetal harm when administered starting at 30 weeks gestation. If the drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to the fetus. Prior to 30 weeks gestation, ZORVOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animals, no evidence of teratogenicity was observed in mouse, rat, or rabbit reproductive studies at doses of diclofenac equivalent to approximately 1 to 2 times the maximum recommended human dose (MRHD) of ZORVOLEX, 105 mg/day.

Data

Animal data
Reproductive studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day, equivalent to the maximum recommended human dose [MRHD] based on a body surface area comparison), and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day; 1 [rats] and 2 [rabbits] times the MRHD on a mg/m^2 basis, respectively) and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice, rats, and humans.

8.2 Labor and Delivery

The effects of ZORVOLEX on labor and delivery in pregnant women are unknown. In rat studies maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased pup survival.

8.3 Nursing Mothers

Based on available data, diclofenac may be present in human milk. One woman treated orally with a diclofenac salt, 150 mg/day, had a milk diclofenac level of 100 mcg/L, equivalent to an infant dose of about 0.03 mg/kg/day. Diclofenac was not detectable in breast milk in 12 women using diclofenac (after either 100 mg/day orally for 7 days or a single 50 mg intramuscular dose administered in the immediate postpartum period). Exercise caution when ZORVOLEX is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of ZORVOLEX in pediatric patients has not been established.

8.5 Geriatric Use

As with any NSAID, caution should be exercised in treating the elderly (65 years and older). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

Diclofenac metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Older age increases the risk for GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population [*see Warnings and Precautions (5.2)*].

10 OVERDOSAGE

Symptoms following acute NSAID overdoses include lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care.

Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

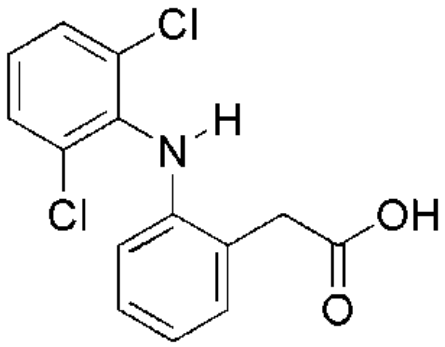
Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen

within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

ZORVOLEX (diclofenac) capsules contain the active ingredient diclofenac which is a benzeneacetic acid based nonsteroidal anti-inflammatory drug (NSAID). ZORVOLEX is available as hard gelatin capsules of 18 mg and 35 mg for oral administration. The chemical name of diclofenac is 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid. The molecular weight is 296.15. Its molecular formula is $C_{14}H_{11}Cl_2NO_2$, and it has the following structural formula.



The inactive ingredients in ZORVOLEX include a combination of lactose monohydrate, sodium lauryl sulfate, microcrystalline cellulose, croscarmellose sodium and sodium stearyl fumarate. The capsule shells contain gelatin, titanium dioxide, and dyes FD&C blue #1, FD&C blue #2, FDA/E172 Yellow Iron Oxide and FDA/E172 Black Iron Oxide. The imprinting on the gelatin capsules is white edible ink. The 18 mg capsules have a blue body imprinted with IP-203 and light green cap imprinted with 18 mg in white ink. The 35 mg capsules have a blue body imprinted with IP-204 and green cap imprinted with 35 mg in white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZORVOLEX is an NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of ZORVOLEX, like that of other NSAIDs, is not completely understood but may involve inhibition of the cyclooxygenase (COX-1 and COX-2) pathways. Diclofenac's mechanism may also be related to prostaglandin synthetase inhibition.

12.3 Pharmacokinetics

The relative bioavailability of ZORVOLEX 35 mg capsules was compared to diclofenac potassium immediate-release (IR) tablets 50 mg in 39 healthy subjects under fasted and fed conditions in a single-dose crossover study.

ZORVOLEX 35 mg capsules do not result in an equivalent systemic exposure to 50 mg diclofenac potassium IR tablets.

When taken under fasted conditions, a 20% lower dose of diclofenac in ZORVOLEX capsules resulted in a 23% lower mean systemic exposure (AUC_{inf}) and a 26% lower mean peak concentration (C_{max}) compared to diclofenac potassium IR tablets. The time to reach peak concentration (T_{max}) was similar for ZORVOLEX and diclofenac potassium IR tablets and was ~1 hour for both.

When taken under fed conditions, a 20% lower dose of diclofenac in ZORVOLEX capsules resulted in a 23% lower mean systemic exposure (AUC_{inf}) and a 48% lower mean C_{max} compared to diclofenac potassium IR tablets. The T_{max} for ZORVOLEX was delayed by approximately 1 hour compared to diclofenac potassium IR tablets (3.32 hours vs. 2.33 hours, respectively).

When taken under fed conditions, ZORVOLEX capsules resulted in an 11% lower mean systemic exposure (AUC_{inf}) and a 60% lower mean C_{max} compared to fasted conditions. Whereas diclofenac potassium IR tablets under fed conditions resulted in 8% - 10% lower mean systemic exposure (AUC_{inf}) and 28% - 43% lower mean C_{max} compared to fasted conditions, based on the results from two individual food effect studies. The T_{max} for ZORVOLEX was delayed by approximately 2.32 hours under fed conditions compared to fasted conditions (3.32 hours vs. 1.00 hour, respectively), while the T_{max} for diclofenac potassium IR tablets was delayed by approximately 1.00 - 1.33 hours under fed conditions compared to fasted conditions (1.70 vs. 0.74 hours and 2.33 vs. 1.00 hours, respectively in two studies).

There were no differences in elimination half-life between ZORVOLEX and diclofenac potassium IR tablets under fasted or fed conditions.

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. After repeated oral administration, no accumulation of diclofenac in plasma occurred.

Administration of ZORVOLEX capsules 18 mg and 35 mg was associated with dose proportional pharmacokinetics.

Taking ZORVOLEX with food causes a significant decrease in the rate but not the overall extent of systemic absorption of diclofenac compared with taking ZORVOLEX on an empty stomach. ZORVOLEX capsules results in 60% lower C_{max}, 11% lower $AUC_{inf,}$ and

2.32 hours delayed T_{max} (1.0 hour during fasted versus 3.32 hours during fed) under the fed condition compared to the fasted condition. The effectiveness of ZORVOLEX when taken with food has not been studied in clinical studies. The decreased C_{max} may be associated with decreased effectiveness. Taking ZORVOLEX with food may cause a reduction in effectiveness compared to taking ZORVOLEX on an empty stomach.

Distribution

The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg. Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 mg/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Elimination

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy-diclofenac is primarily mediated by CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Specific Populations

Age: Pediatric Population: The pharmacokinetics of ZORVOLEX has not been investigated in pediatric patients.

Race/Ethnicity: Pharmacokinetic differences due to race/ethnicity have not been identified.

Renal Impairment: Diclofenac pharmacokinetics has been investigated in subjects with renal insufficiency. No differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal impairment. In patients with renal impairment (inulin clearance 60-90, 30-60, and less than 30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects.

Hepatic Impairment: No dedicated diclofenac pharmacokinetics studies in patients with hepatic impairment were conducted. Hepatic metabolism accounts for almost 100% of diclofenac elimination. Therefore, in patients with hepatic impairment, start with the lowest dose and if efficacy is not achieved, consider use of an alternate product.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (0.2-fold the maximum recommended human dose [MRHD] of ZORVOLEX based on body surface area comparison) have revealed no significant increase in tumor incidence. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.014-fold the MRHD based on body surface area comparison) in males and 1 mg/kg/day (0.04-fold the MRHD based on body surface area comparison) in females did not reveal any oncogenic potential.

Mutagenesis: Diclofenac sodium did not show mutagenic activity in in vitro point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian in vitro and in vivo tests, including dominant lethal and male germinal epithelial chromosomal aberration studies in Chinese hamsters.

Impairment of Fertility: Diclofenac sodium administered to male and female rats at 4 mg/kg/day (0.4-fold the MRHD based on body surface area comparison) did not affect fertility.

14 CLINICAL STUDIES

Phase 3 Efficacy Study in Patients with Acute Pain

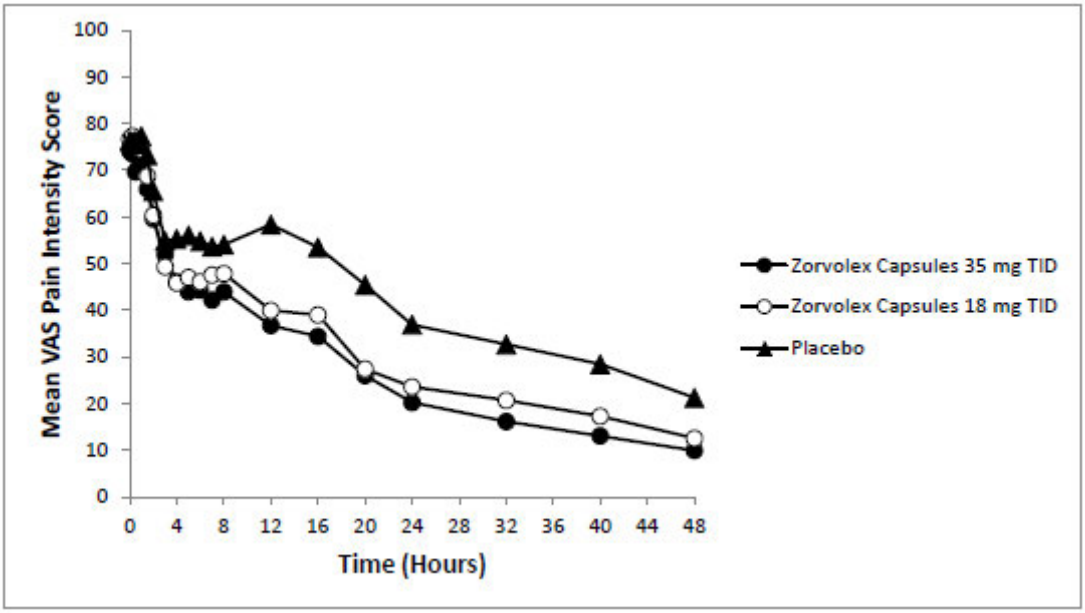
The efficacy of ZORVOLEX in the management of acute pain was demonstrated in a single multicenter, randomized, double-blind, placebo-controlled, parallel arm study comparing ZORVOLEX 18 mg and 35 mg taken three times a day, placebo, and celecoxib in patients with pain following bunionectomy. The study enrolled 428 patients with a mean age of 40 years (range 18 to 65 years) and a minimum pain intensity rating of at least 40 mm on a

100-mm visual analog scale (VAS) during the 9-hour period after discontinuation of the anesthetic block following bunionectomy surgery. Patients were randomized equally across the treatment groups.

The mean and range (in parenthesis) of pain intensities on the VAS at baseline were 74 mm (44 to 100 mm), 77 mm (41 to 100 mm), and 76 mm (40 to 100 mm) for the ZORVOLEX 35 mg, ZORVOLEX 18 mg, and placebo groups, respectively. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as rescue medication. About 82% of patients in the ZORVOLEX 35 mg group, 85% of the patients in the ZORVOLEX 18 mg group, and 97% of patients in the placebo group took rescue medication for pain management during the study.

The average pain intensities over time are depicted for the treatment groups in Figure 1. Both ZORVOLEX 18 mg and 35 mg demonstrated efficacy in pain intensity reduction compared with placebo, as measured by the sum of pain intensity difference over 0 to 48 hours after the first dose.

Figure 1 Average Pain Intensity Over 48 Hours for ZORVOLEX 18 mg, ZORVOLEX 35 mg, and Placebo Groups



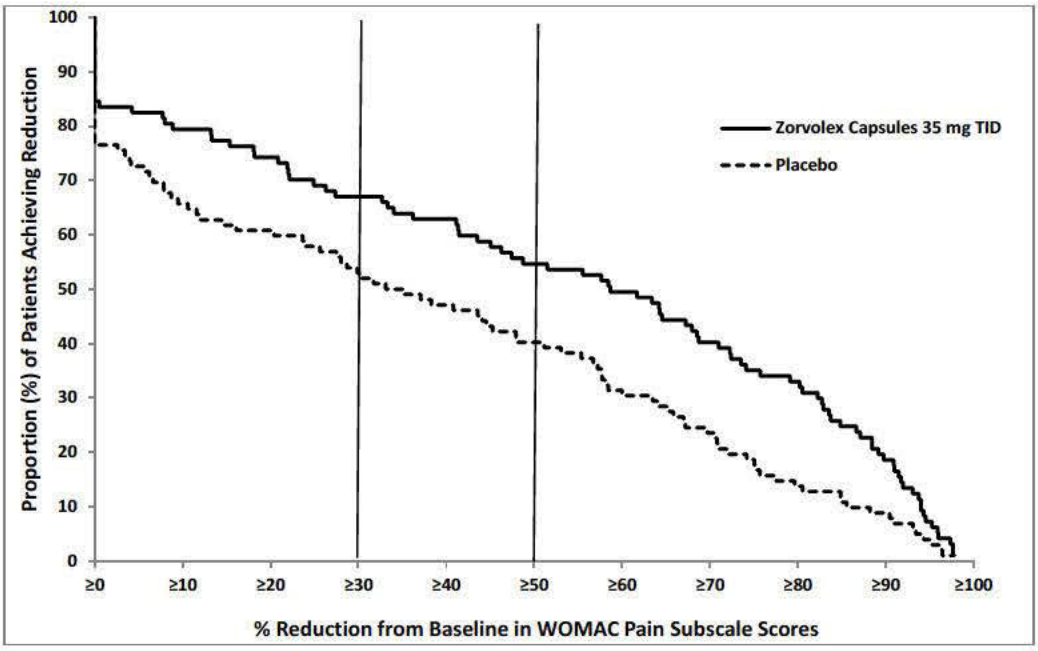
Phase 3 Efficacy Study in Patients with Osteoarthritis Pain

The efficacy of ZORVOLEX in the management of osteoarthritis pain was demonstrated in a single multicenter, randomized, double-blind, placebo-controlled, parallel-arm study comparing ZORVOLEX 35 mg taken twice a day or three times a day and placebo in patients with osteoarthritis of the knee or hip. The study enrolled 305 patients with a mean age of

62 (range 41 to 90 years). Osteoarthritis pain was measured using the Western Ontario and McMaster University Osteoarthritis Index Pain Subscale (WOMAC Pain Subscale). Mean baseline WOMAC Pain Subscale Score across treatment groups was 75 mm using a 0 to 100 mm visual analog scale.

The primary efficacy parameter was the change from baseline at 12 weeks in the WOMAC Pain Subscale. ZORVOLEX 35 mg three times a day reduced osteoarthritis pain compared with placebo, as measured by WOMAC Pain Subscale Score. The distribution (%) of patients achieving various percentage reductions in pain intensity at Week 12 are depicted in Figure 2.

Figure 2 Distribution (%) of Patients Achieving Various Percentage Reductions in Pain Intensity at Week 12



16 HOW SUPPLIED/STORAGE AND HANDLING

ZORVOLEX (diclofenac) capsules are supplied as:

- 18 mg - blue body and light green cap (imprinted IP-203 on the body and 18 mg on the cap in white ink)
  - NDC (42211-203-23), Bottles of 30 capsules
  - NDC (42211-203-29), Bottles of 90 capsules

- 35 mg - blue body and green cap (imprinted IP-204 on the body and 35 mg on the cap in white ink)
  - NDC (42211-204-23), Bottles of 30 capsules
  - NDC (42211-204-29), Bottles of 90 capsules

Storage

Store at 25ºC (77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF). [See USP Controlled Room Temperature]

Store in the original container and keep the bottle tightly closed to protect from moisture. Dispense in a tight container if package is subdivided.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (NSAID Medication Guide).

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

Cardiovascular Effects
Advise patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up [*see Warnings and Precautions (5.1)*].

Gastrointestinal Effects
Advise patients to be alert for the signs and symptoms of ulcerations and bleeding, and to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Inform patients of the importance of this follow-up [*see Warnings and Precautions (5.2)*].

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop therapy and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Adverse Skin Reactions
Advise patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible [*see Warnings and Precautions (5.8)*].

Weight Gain and Edema
Advise patients to promptly report to their physicians signs or symptoms of unexplained weight gain or edema during treatment with ZORVOLEX [*see Warnings and Precautions (5.5)*].

Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Warnings and Precautions (5.7)*].

Effects During Pregnancy

Advise female patients to inform their prescriber if pregnant or planning to become pregnant [*see Use in Specific Populations (8.1), Warnings and Precautions (5.9)*].

Manufactured (under license from iCeutica Pty Ltd.) for and Distributed by:
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

U.S. Patent No. 8,679,544

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding, **talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain

- flu-like symptoms
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines requiring a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex®
Diclofenac	Flector®, Cataflam®, Voltaren®, Arthrotec® (combined with misoprostol), PENNSAID®, Zorvolex®, Cambia™, Voltaren® gel, Zipsor®
Diflunisal	Dolobid®
Etodolac	Lodine®, Lodine XL®
Fenoprofen	Nalfon®, Nalfon® 200
Flurbiprofen	Ansaid®
Ibuprofen	Motrin®, Tab-Profen®, *Vicoprofen® (combined with hydrocodone), Combunox™ (combined with oxycodone), Duexis® (combined with famotidine)
Indomethacin	Indocin®, Indocin SR®, Indo-Lemmon™, Indomethagan™, Tivorbex™
Ketoprofen	Oruvail®
Ketorolac	Toradol®, SPRIX®
Mefenamic Acid	Ponstel®
Meloxicam	Mobic®
Nabumetone	Relafen®

Naproxen	Naprosyn®, Anaprox®, Anaprox® DS, EC-Naprosyn®, Naprelan®, Naprapac® (copackaged with lansoprazole), Treximet® (combined with sumatriptan succinate) and Vimovo® (combined with esomeprazole magnesium)
Oxaprozin	Daypro®
Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin DS®, Tolectin® 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

The brands listed are the trademarks or registered marks of their respective owners.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured (under license from iCeutica Pty Ltd) for and Distributed by:
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Issued: August 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement #	204592/002
Applicant Name	Iroko Pharmaceuticals
Date of Submission	October 31, 2013
PDUFA Goal Date	August 31, 2014
Proprietary Name / Established (USAN) Name	Zorvolex /Diclofenac
Dosage Forms / Strength	Capsules, 18 mg and 35 mg
Proposed Indication(s)	1. For the treatment of mild to moderate acute pain 2. For the management of the pain of osteoarthritis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Steven Galati, MD
Statistical Review	David Petullo, MS, Janice Derr, PhD
OSI	Cynthia Kleppinger, MD, Janice Pohlman, MD, MPH
CDTL Review	Joshua Lloyd, MD
Other	

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This application is an efficacy supplement for Zorvolex, an immediate-release capsule formulation of diclofenac acid approved for the management of mild to moderate acute pain on October 20, 2013. The referenced product was NDA 020142, Cataflam Tablet, an immediate-release formulation of diclofenac potassium indicated for the treatment of primary dysmenorrhea, relief of mild to moderate pain, and relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis; all in adults. The Applicant developed Zorvolex as a new formulation of diclofenac with reduced particle size, intended to promote the dissolution and absorption of diclofenac. However, the absorption of diclofenac from Cataflam is nearly 100% following oral administration. The Applicant claimed that the improved dissolution properties of Zorvolex would be associated with rapid absorption resulting in comparable pain relief to Cataflam at an approximately 20% lower dose, although they have not conducted any studies with Cataflam as an active comparator.

The current application is intended to support a new indication, the management of the pain of osteoarthritis. One adequate and well-controlled trial was submitted in support of the new indication. The key issue that will be discussed in this review is the difference in the Agency's and the Applicant's interpretation of the efficacy findings and how that relates to the proposed dosing regimen.

2. Background

The Applicant conducted the clinical development program under IND 103,880. The currently approved dosing for acute pain is 18 mg or 35 mg, three times daily. This efficacy supplement is supported by a 12-week adequate and well-controlled efficacy study and a 52-week open-label safety study that was the subject of special protocol assessments, although no agreement was reached due to statistical considerations, along with relying, in part, on the Agency's prior finding of efficacy and safety of Cataflam. The Division discussed the data necessary to support an indication for the management of the pain of osteoarthritis and for the relief of the signs and symptoms of osteoarthritis, the former relying on one endpoint, pain intensity, and the latter requiring prespecified analysis of three primary endpoints, pain, function, and patient global, with appropriate statistical methods to address the multiple endpoints. The Applicant has opted to seek an indication for the management of the pain of osteoarthritis.

3. CMC/Device

No new CMC data were submitted in support of this application. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in support of this application. There are no outstanding issues.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data were submitted in support of this application. There are no outstanding issues.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

A single Phase 3, randomized, double-blind, placebo-controlled, parallel group efficacy trial was conducted comparing 35 mg of Zorvolex twice daily, three times daily and placebo in patients with osteoarthritis pain involving the knee or hip. Subjects were 40 years of age and older, with a baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score of at least 40 mm and had at least a 15 mm increase after being taken off their prior medication. The WOMAC pain subscale score consists of an average of five questions regarding pain during walking, using the stairs, in bed, sitting or lying, and standing rated on a 100 mm VAS scale with 0 being no pain and 100 the worst possible pain. Rescue medication was available as acetaminophen 500 mg, with a daily maximum of 3 grams. No rescue medication was to have been used within 12 hours of an efficacy assessment. Study drug was dosed on an empty stomach. The primary efficacy analysis was the mean change from baseline in WOMAC pain subscale at Week 12, and secondary analyses included the mean change in WOMAC pain subscale from baseline to Weeks 2 and 6, mean change in WOMAC function subscale, patient global impression of change, amount of rescue medication taken, a continuous responder function, and a number of additional analyses.

Three-hundred five patients were randomized and 47 discontinued early. The disposition is shown in the following table from Mr. Petullo's review. Adverse events were the most

common reason for early discontinuation, occurring more frequently in the active treatment groups, and lack of efficacy was the next most common, most frequent in the placebo group.

Table 1 Disposition, Study DIC3-08-05

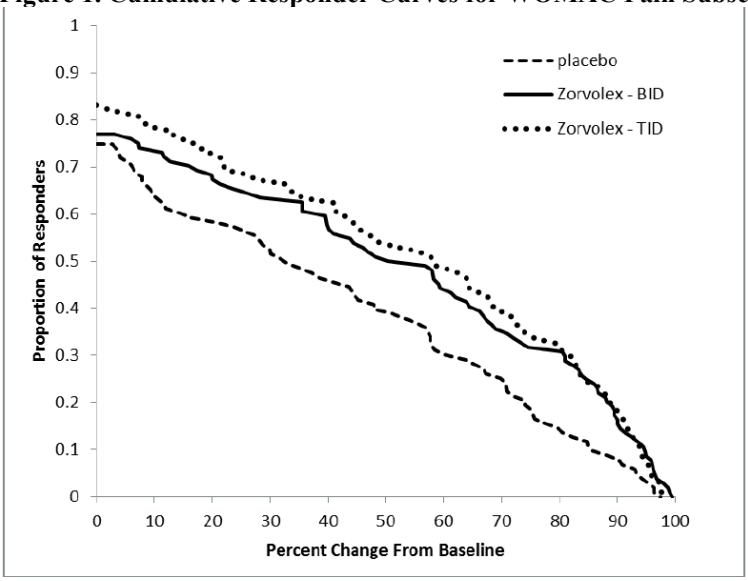
Disposition	placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
Randomized	103	104	98
Completed	86	91	81
discontinued	17	13	17
Reason for Discontinuation			
adverse event	4	9	12
lack of efficacy	6	2	-
withdrawal of consent	2	1	3
protocol violation	2	1	2
lost to follow-up	3	-	-

Demographic characteristics were fairly evenly distributed; most subjects were female and white. Baseline scores were similar.

The results demonstrated a statistically significantly larger reduction in pain for the Zorvolex 35 mg three times daily group as compared to placebo. The Zorvolex 35 mg twice daily group had a numerically larger, but not statistically significant, reduction in pain compared to the placebo group. Mr. Petullo confirmed the efficacy results. The Applicant considered a pain subscale score obtained within 12 hours of rescue missing data for their analysis and used a statistical methodology that assumed the data were missing at random. Mr. Petullo disagreed with the missing at random assumption used by the Applicant and conducted a number of analyses, including analyses that attributed poor scores for missing data due to early discontinuations. Mr. Petullo was able to confirm a finding of efficacy for the Zorvolex 35 mg three times daily group, when compared to placebo, but not the Zorvolex twice daily group. Additional analyses submitted by the Applicant were methodologically problematic; for example, excluding a placebo patient with a good response, and using scores after the use of rescue medication, rather than collecting pain scores prior to the use of rescue.

A cumulative responder function was calculated by Mr. Petullo and was supportive of efficacy for the Zorvolex 35 mg three times daily group, as shown in the following figure from his review.

Figure 1. Cumulative Responder Curves for WOMAC Pain Subscale Score



Secondary analyses were generally supportive of the primary analysis, including the results at Week 2 and Week 6. While findings for the WOMAC function subscale and patient global impression of change scales favored the active treatment groups, failure to incorporate adequate statistical methods for handling multiplicity, as recommended by the Division during development, preclude including these outcomes in the labeling.

Overall, the results of this study support a finding of efficacy for Zorvolex 35 mg three times daily for the pain of osteoarthritis.

8. Safety

The safety database in support of this application consisted of the 305 patients enrolled in the efficacy study and 601 subjects enrolled in a 52-week open-label safety study. A total of 705 unique subjects were treated with Zorvolex 35 mg twice daily and three times daily. Of these 705, 426 were on Zorvolex for at least 6 months, 161 of whom were on the three times daily dose. Three hundred and seventy-three subjects were on Zorvolex for at least 11 months, 83 of whom were on the three times daily dose. As discussed by Drs. Lloyd and Galati, the total number of subjects exposed to the three times daily dosing regimen that demonstrated efficacy and will be the recommended dose in labeling was below the requested number of at least 300 patients treated for at least 6 months and at least 100 patients treated for at least 1 year. However, I agree with their rationale for this exposure being adequate based on, "1) the known safety profile of diclofenac, 2) the exposure for the combined BID and TID dosing regimens exceeds the safety database requirements, and 3) the Cmax and systemic exposure for the proposed product is lower than the reference product." There are also no excipients in the formulation that would be expected to alter the toxicity of the product.

During the efficacy study and open-label safety study, there were no deaths. In the efficacy study, serious adverse events were reported in seven subjects who received Zorvolex and two

subjects who received placebo. In the active arms, the events were each reported once and included ALT increased, AST increased, DVT, pulmonary embolism, COPD, three different metastases, one malignant melanoma, non-cardiac chest pain, and a case of appendicitis. The elevated liver enzymes are known adverse events that can be caused by diclofenac. The others are unlikely to have been related to study participation. In the open-label safety study, 42 subjects had serious adverse events, any occurring in at least 2 subjects are displayed in the following table from Dr. Galati's review.

Table 2 Serious Adverse Events in the Open-label Study

Preferred Term	Zorvolex Capsules 35 mg tid[a] N=373 n (%)	Zorvolex Capsules 35 mg bid[b] N=655 n (%)	Combined Zorvolex Capsules 35 mg[c] N=705 n (%)
Any SAE	19 (5.1)	29 (4.4)	48 (6.8)
Chronic obstructive pulmonary disease	0	3 (0.5)	3 (0.4)
Osteoarthritis	1 (0.3)	2 (0.3)	3 (0.4)
Carotid artery stenosis	0	2 (0.3)	2 (0.3)
Chest pain	0	2 (0.3)	2 (0.3)
Diverticulitis	1 (0.3)	1 (0.2)	2 (0.3)
Lumbar spinal stenosis	1 (0.3)	1 (0.2)	2 (0.3)
Myocardial infarction	0	2 (0.3)	2 (0.3)
Pulmonary embolism	2 (0.5)	0	2 (0.3)

Source: 5.3.5.3 Integrated Summary of Safety, Table 14.3.2.2.2

The occurrence of two myocardial infarctions may have been related to exposure to diclofenac, but there is already a cardiovascular thromboembolic warning in the labeling for Zorvolex. The remainder are unlikely to have been associated with diclofenac.

Looking at the entire safety population, there were additional cases of angina and coronary artery disease as shown in a section of the Applicant's Table below. The serious gastrointestinal events did not include any cases of hemorrhage, and it is difficult to know if the diclofenac contributed to the diverticular perforation.

Table 3 Cardiac and Gastrointestinal Serious Adverse Events, Safety Population

Table 14.3.2.2.1
Summary of Serious Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Diclofenac Nanoformulation Capsule 35 mg TID [1] (N=373)		Diclofenac Nanoformulation Capsule 35 mg BID [2] (N=655)		Combined Diclofenac Nanoformulation [3] (N=705)		Placebo (N=103)	
Any Serious AE	19	(5.1%)	29	(4.4%)	48	(6.8%)	3	(2.9%)
CARDIAC DISORDERS	2	(0.5%)	5	(0.8%)	7	(1.0%)	0	
Angina pectoris	1	(0.3%)	0		1	(0.1%)	0	
Angina unstable	1	(0.3%)	0		1	(0.1%)	0	
Atrial fibrillation	0		1	(0.2%)	1	(0.1%)	0	
Coronary artery disease	0		1	(0.2%)	1	(0.1%)	0	
Coronary artery stenosis	0		1	(0.2%)	1	(0.1%)	0	
Myocardial infarction	0		2	(0.3%)	2	(0.3%)	0	
GASTROINTESTINAL DISORDERS	1	(0.3%)	6	(0.9%)	7	(1.0%)	0	
Abdominal hernia	0		1	(0.2%)	1	(0.1%)	0	
Colitis	0		1	(0.2%)	1	(0.1%)	0	
Diverticular perforation	0		1	(0.2%)	1	(0.1%)	0	
GASTROINTESTINAL DISORDERS								
Gastrointestinal pain	0		1	(0.2%)	1	(0.1%)	0	
Intestinal strangulation	0		1	(0.2%)	1	(0.1%)	0	
Pancreatitis	0		1	(0.2%)	1	(0.1%)	0	
Small intestinal obstruction	1	(0.3%)	0		1	(0.1%)	0	
HEPATOBILIARY DISORDERS	0		1	(0.2%)	1	(0.1%)	0	
Bile duct stone	0		1	(0.2%)	1	(0.1%)	0	

Oddly, there was a case of Hy's law reported that did not make it into the reporting of serious adverse events, but was described under early discontinuations. A 60 year old woman with a hstory of osteoarthritis in the open-label safety study, who was treated with Zorvlex 35 mg twice daily for a week and then three times daily for approximately 5.5 months, was found to have elevated liver enzyme levels that met the criteria for Hy's Law as shown in the following Table from Dr. Galati's review. Following discontinuation of Zorvolex, the liver enzyme levels returned to normal. There were no associated symptoms and no other suspect medications. This finding is a known risk with diclofenac and there is a warning in the labeling.

Table 4 Liver Enzyme Levels, Subject 119-003.

Date (Visit)	Alkaline Phosphatase (42-98 U/L)	ALT (0-33 U/L)	AST (14-34 U/L)	Total Bilirubin (5.13-20.52 µmol/L)
16JAN2012 (Screening)	104[a]	27	25	8.6
21FEB2012 (Week 4)	186[a,b]	58[a]	77[a]	6.8
20MAR2012 (Week 8)	121[a]	27	31	8.6
17APR2012 (Week 12)	126[a]	73[a]	54[a]	10.3
10JUL2012 (Week 24)	236[a,b]	736[a,b]	992[a,b]	112.9[a,b]
16JUL2012 (Week 52/ET)	268[a,b]	947[a,b]	1507[a,b]	241.1[a,b]
23JUL2012 (Unscheduled)	224[a,b]	669[a,b]	1154[a,b]	335.2[a,b]
07AUG2012 (Unscheduled)	162[a,b]	162[a,b]	239[a,b]	177.8[a,b]
28AUG2012 (Unscheduled)	91	25	47[a]	63.3[a,b]

Data source: Appendix 16.2.8, Listing 16.2.14.1.2

Treatment emergent adverse events were reported in 45% of patients in the placebo group, 48% in Zorvolex twice daily group, and 60% in the Zorvolex thrice daily group. The most common adverse events were nausea, diarrhea, headache, abdominal pain, vomiting, ALT increased, dyspepsia, and creatinine increased. The treatment emergent adverse events in the open-label study were similar. As with the acute pain development program, the Applicant has not conducted any studies to evaluate the relative safety of Zorvolex with Cataflam or any other diclofenac product. Therefore, no comparative claims may be made.

Overall, the adverse event profile of Zorvolex is consistent with the adverse event profile for diclofenac. There was no reason to suspect otherwise, given the dosing regimen does not exceed the exposure by the referenced product, Cataflam.

9. Advisory Committee Meeting

No advisory committee meeting was necessary for this efficacy supplement.

10. Pediatrics

A waiver for the pediatric study requirements under the Pediatric Research Equity Act was granted given that studies would be highly impractical or impossible due to the extremely limited incidence of OA in the pediatric population with concurrence from the Pediatric Research Committee.

11. Other Relevant Regulatory Issues

Two clinical sites for the efficacy study were inspected and were found to have complied with applicable regulations.

Adequate certification regarding financial disclosures was submitted and no investigators were found to have financial interests or arrangements to disclose.

The application was presented at a 505(b)(2) clearance meeting on July 7, 2014, and no problems were identified.

There are no other unresolved relevant regulatory issues

12. Labeling

The Division of Medication Error Prevention and Analysis evaluated the proposed changes to the insert labeling, and requested no edits beyond those implemented by the Division. Comments from the Office of Prescription Drug Promotion were conveyed to the Applicant. There was discussion between the Applicant and the Division regarding labeling for the 35 mg (b) (4) dose. The Applicant argued that, because the adverse events associated with diclofenac are generally dose related, prescribers should have information (b) (4) However, In the absence of an adequate finding of efficacy associated with the (b) (4) dosing regimen, no adverse events are justified. Concurrence was reached on the final labeling of the new indication with the 35 mg three timed daily dosing regimen.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

  There was adequate evidence of efficacy demonstrated for the Zorvolex 35 mg three times daily dosing regimen for the indication of the management of the pain of osteoarthritis. The overall safety profile was consistent with the referenced drug, Cataflam. No unexpected findings occurred. There was a Hy's law case of elevated liver enzymes that resolved after Zorvolex was discontinued. This is concerning and serves as a reminder that, while NSAIDs such as diclofenac do not have the risks of respiratory depression, sedation, and addiction associated with opioid analgesics, serious risks are associated with the class. Zorvolex and other NSAIDs are labeled with warnings for cardiovascular thromboembolic events, gastrointestinal hemorrhage, ulceration and perforation, liver injury, hypertension, congestive heart failure, renal injury, serious skin reactions, effects during pregnancy, and effects in patients with asthma.

- Recommendation for Postmarketing Risk Management Activities

There is no need for postmarketing risk management activities beyond the usual postmarketing surveillance.

- Recommendation for other Postmarketing Study Commitments

There is no need for any postmarketing study commitments.

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/s/

SHARON H HERTZ
08/22/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 204592/S-002

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Steven Galati
Josh Lloyd
David Petullo
Janice Derr
Cynthia F. Kleppinger
Janice Pohlman
James Schlick
Irene Chan
Ramesh Raghavachari
Barbara Fuller
Lashawn Griffiths
Eunice Chung-Davies
Swati Patwardhan
Sharon Hertz
Bob Rappaport

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 7, 2014
From	Joshua M. Lloyd, MD Clinical Team Leader, DAAAP
Subject	Cross-Discipline Team Leader Review
NDA# **Supplement#**	204-592 002
Applicant	Iroko Pharmaceuticals, LLC
Date of Submission	October 31, 2013
PDUFA Goal Date	August 31, 2014
Proprietary Name / **Established (USAN) names**	Zorvolex / Diclofenac
Dosage forms / Strength	Oral Capsules / 35 mg
Proposed Indication(s)	Management of osteoarthritis pain
Recommended:	Approval of the 35 mg TID dosing regimen

1. Introduction

Iroko Pharmaceuticals, LLC ("Applicant") submitted this supplemental New Drug Application (sNDA) for Zorvolex capsules to add the indication, for the treatment of osteoarthritis (OA) pain. Zorvolex capsules, an immediate-release formulation of diclofenac, were approved in 18 mg and 35 mg strengths, on October 18, 2013, for the treatment of mild to moderate acute pain in adults. The Applicant conducted the clinical development program under IND 103,880 and proposes to market the 35 mg strength to be taken (b) (4) three times daily for the treatment of osteoarthritis pain.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities and is a potent inhibitor of both COX-1 and COX-2. Diclofenac is approved and marketed in the United States as various salt and free acid forms in oral (immediate-release and modified-release) and topical formulations for multiple painful conditions. The Applicant submitted this sNDA for Zorvolex under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referencing the approved product Cataflam (diclofenac potassium; NDA 020142; Novartis Pharmaceuticals Corporation). Cataflam is approved for treatment of primary dysmenorrhea, relief of mild to moderate pain, and relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis; all in adults.

This sNDA consists of clinical data from one pivotal Phase 3 clinical trial (DIC3-08-05) and one Phase 3 long-term open-label safety study (DIC3-08-06) to support use in the proposed indication, treatment of osteoarthritis pain. No additional chemistry, manufacturing, and controls (CMC); nonclinical; or clinical pharmacology data were submitted with this sNDA.

This sNDA submission was given a standard review designation. I have concluded that this application should receive an Approval action and have discussed my reasons for this decision in Section 13 below. This review will cover the safety and efficacy of Zorvolex capsules for use in patients with osteoarthritis pain.

2. Background

Zorvolex 18 mg and 35 mg capsules were recently approved on October 18, 2013, as a 505(b)(2) NDA, for the treatment of mild to moderate acute pain. The Applicant initially developed Zorvolex as a new formulation of diclofenac (in the free acid form) with reduced particle size and increased relative drug particle surface area to, according to the Applicant, promote the dissolution and absorption of diclofenac. The Applicant further purported that the improved dissolution properties of Zorvolex are associated with rapid absorption resulting in comparable pain relief to Cataflam tablets at an approximately 20% lower dose and that the lower dose may have the potential for an improved safety profile compared to Cataflam. However, it is uncertain how any potentially improved dissolution properties will substantially improve upon the absorption of diclofenac as Cataflam is completely absorbed (100%) following oral administration, with mean peak concentrations appearing within one hour. The Applicant states that they are developing Zorvolex capsules 35 mg to address a need for lower-dose diclofenac options for the treatment of OA pain. The Applicant has not provided any data, in the acute pain application or the current application, comparing Zorvolex to Cataflam upon which to make any comparative safety or efficacy claims or to substantiate their rationale.

The Division held End-of-Phase 2 and Pre-NDA meetings with the Applicant during clinical development where agreement was reached on the overall design of the clinical development program for OA. One positive adequate and well-controlled clinical efficacy trial of 12-weeks duration in patients with osteoarthritis may support this indication given that the Applicant was relying, in part, on previous findings of safety and efficacy for Cataflam for this 505(b)(2) application. A safety database that includes at least 300 patients treated for at least 6 months and at least 100 patients treated for at least 1 year is required. The Applicant's Phase 3 clinical trial in OA was the subject of two Special Protocol Assessments (SPAs). Although no agreement was reached on the SPAs (primarily for statistical reasons surrounding the handling of missing data), the Division did agree with the overall study design, including the proposed flare design. The Division noted that the proposed study would only support an efficacy claim for the treatment of OA pain and that if the Applicant wanted to pursue an indication for the relief of the signs and symptoms of OA, they must demonstrate efficacy on three primary endpoints, including an analysis of the mean changes from baseline in pain, function, and patient global with appropriate statistical methods to address the multiple endpoints. In response to advice the Applicant received from the Division for another OA product regarding recent changes in thinking about the appropriateness of a flare design in OA studies, the Division held a Type A clinical guidance meeting with the Applicant where the Division agreed that, since the pivotal clinical trial in OA utilizing a flare design was already underway,

it is acceptable for the study to continue utilizing a flare design without amending the protocol and that this design would be acceptable for this study intended to support efficacy for the proposed product.

3. CMC/Device

The CMC review was conducted by Donald Klein, PhD, with secondary concurrence by Ramesh Raghavachari, PhD. No additional CMC data were submitted with this sNDA. The Applicant submitted a request for categorical exclusion from conducting an environmental assessment, and CMC found this request acceptable. The CMC review team recommends this application for approval.

4. Nonclinical Pharmacology/Toxicology

No additional nonclinical pharmacology/toxicology data were submitted with this sNDA.

5. Clinical Pharmacology/Biopharmaceutics

No additional clinical pharmacology or biopharmaceutics data were submitted with this sNDA. Please refer to my review dated September 30, 2013, for a discussion of the relative bioavailability between Zorvolex and the reference product (i.e., Cataflam), dose proportionality, and a description of the food effect.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The efficacy portion of this NDA review was conducted by Steven Galati, MD, with secondary concurrence by me. The statistical review was conducted by David Petullo, MS, with secondary concurrence by Janice Derr, PhD.

The Applicant submitted the results of one pivotal Phase 3 clinical trial (DIC3-08-05) as evidence of efficacy for Zorvolex for the management of osteoarthritis pain. Dr. Galati conducted a full review of Study DIC3-08-05, as this is the pivotal trial intended to demonstrate efficacy for Zorvolex in osteoarthritis pain. I will review the salient study design features and results below.

Study DIC3-08-05

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, Parallel-Group, Efficacy and Safety Trial of Diclofenac Nanoformulation Capsules in Subjects with Osteoarthritis of the Knee or Hip

Location: United States

Objective: To evaluate the analgesic efficacy and safety of Zorvolex capsules 35 mg administered twice and three times daily compared to placebo

Design: Phase 3, randomized, double-blind, fixed-dose, parallel-group, placebo-controlled, multicenter, clinical trial

Duration: 12 weeks of study drug treatment

Population: Male and female patients, ≥40 years of age, with osteoarthritis of the hip or knee[1] who have a WOMAC pain subscale score ≥40 mm (on a 0 to 100 mm visual analog scale [VAS]) at baseline and had a ≥15 mm increase in the WOMAC pain subscale VAS score from screening at baseline (OA pain flare)

Treatment: Patients were randomized in a 1:1:1 fashion to the following treatment groups. Study drug (active or placebo) was administered four times daily to maintain the blind. Study drug was to be given on an empty stomach throughout the 12-week treatment period.

- Zorvolex 35 mg twice daily (BID)
- Zorvolex 35 mg three times daily (TID)
- Placebo

Rescue Medication: Acetaminophen 500 mg every 4 to 6 hours as needed (maximum 3,000 mg per day); rescue medication was prohibited within 12 hours of the efficacy assessments (Visits 3 [Week 2], 4 [Week 6], and 5 [Week 12])

Primary Efficacy Variable: Mean change from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score at Week 12 or the Early Termination Visit

Secondary Efficacy Variables (none identified as key secondary variables):

- Mean change from Baseline in the WOMAC Pain Subscale score at Week 2 and Week 6

[1] For hip OA, subjects must have articular hip pain and radiographic severity grade II to III (Kellgren-Lawrence). For knee OA, subjects must have knee pain, radiographic severity grade II to III (Kellgren-Lawrence), and at least 1 of the following 3 criteria: 1) age greater than 50 years; 2) morning stiffness < 30 minutes in duration; 3) crepitus

- Mean change from Baseline in the WOMAC Pain Subscale score over the 12-week average
- Mean change from Baseline in the Total (Composite) WOMAC score over the 12-week average
- Mean change from Baseline in the VAS pain intensity over the 12-week average
- Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) scores at Week 12/early termination
- Amount of rescue medication taken by each subject
- Cumulative discontinuations due to lack of efficacy at Week 12
- Mean changes from Baseline in the 2 summary scores (mental component score [MCS] and physical component score [PCS]) of the 36-item short form health survey (SF-36v2™) at Week 12/early termination
- Responder rates for subjects with at least 30% and for subjects with at least 50% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12), as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS pain intensity scores
- Responder rates for subjects who achieved a reduction in pain, evaluated at a continuous cutoff ranging from 0% to 100% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12), as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS pain intensity scores (NOTE: all subjects who withdrew early from the trial were considered nonresponders).

Post-hoc Efficacy Analyses (refer to Dr. Galati's review for a comprehensive list):

- Mean change from Baseline in WOMAC function subscale score, WOMAC stiffness subscale score, and total (composite) WOMAC scores at each scheduled visit (and over the 12-week period if not previously performed as part of the prespecified analysis)

Statistical Methodologies: Mr. Petullo notes in his review that:

> The analysis dataset defined by the applicant was all randomized subjects who received at least one dose of study drug. The primary efficacy endpoint was defined as the mean change from baseline in the WOMAC pain subscale score at Week 12 or early termination. At least four of the five pain subscale questions had to be answered for the score to be considered valid, otherwise, the assessment was considered missing in the analysis. If a subject used rescue medication within 12 hours of an efficacy assessment, the score at that visit was considered missing in the analysis. Results were compared between treatment groups using a mixed model repeated measure (MMRM) analysis with no imputation of missing data. To adjust for multiplicity, the TID dose was compared to placebo and if significant, the BID dose was compared to placebo. Secondary endpoints were analyzed according to the type [of] endpoint. Continuous endpoints utilized an analysis of covariance model (ANCOVA) with treatment, site, gender, and the baseline measure in the model. Ordinal endpoints used a Cochran-Mantel-Haenszel (CMH) test for

comparisons. There was no testing strategy for the secondary endpoints to account for multiplicity.

To examine the missing at random (MAR) assumption in the primary analysis the applicant conducted several sensitivity analyses. These included graphical assessment of WOMAC pain subscale scores for dropouts, an MMRM analysis where dropouts were penalized, ANCOVA with baseline observation carried forward (BOCF) and last observation carried forward (LOCF), and multiple imputation using a pattern mixture framework.

Overall, the statistical methodologies utilized by the applicant for the analyses of the primary and secondary efficacy outcomes were acceptable. However, their primary analysis assumed an MAR assumption which is not valid in this clinical setting. My concern is that a patient on active drug may have discontinued treatment due to an adverse event. In the MAR setting this patient may receive a treatment benefit in the analysis. I focused on an analysis where the pain score for discontinued subjects returned to baseline. Since all subjects had a baseline score prior to starting treatment, I randomly assigned a baseline score from this distribution of scores. I also considered BOCF and a modified BOCF/LOCF approach where I used LOCF for placebo subjects and BOCF for subjects on active drug.

Patient Disposition, Demographics, and Baseline Characteristics:

A total of 305 subjects were randomized and treated, including 103 subjects in the placebo group, 104 subjects in the Zorvolex 35 mg BID group, and 98 subjects in the Zorvolex 35 mg TID group. There were 47 subjects who discontinued from the study, as summarized in the table below. As expected, there are more discontinuations for lack of efficacy in the placebo group than the Zorvolex groups and there are more discontinuations for adverse events in the Zorvolex groups than the placebo group. Notably, two subjects discontinued for lack of efficacy in the Zorvolex 35 mg BID group, whereas none did in the Zorvolex 35 mg TID group. This latter finding is consistent with the overall study results which did not demonstrate a statistically significant treatment effect for the Zorvolex 35 mg BID group (see results below).

Table 1. Disposition for All Randomized Subjects

Disposition	placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
Randomized	103	104	98
Completed	86	91	81
discontinued	17	13	17
Reason for Discontinuation			
adverse event	4	9	12
lack of efficacy	6	2	-
withdrawal of consent	2	1	3
protocol violation	2	1	2
lost to follow-up	3	-	-

Source: Table 2 from Mr. Petullo's review

Dr. Galati reviewed the cases for subjects who discontinued due to "withdrawal of consent" and found no underlying drug-related safety issues that contributed to discontinuation.

Demographics for all randomized and treated patients are shown in the table below. The study enrolled mostly Caucasian subjects with a female predominance, and this finding is consistent across treatment groups. Treatment groups were generally balanced with respect to demographics.

Table 2. Demographics for All Randomized Subjects

Characteristic	placebo	Zorvolex 35mg BID	Zorvolex 35 mg TID
Number of Patients	103	104	98
Age in years			
Mean (SD)	62 (8.4)	61 (8.3)	62 (9.9)
Median	61	60	61
[range]	[45, 82]	[46, 86]	[41, 90]
Gender, n (%)			
Female	71 (69)	64 (62)	68 (69)
Male	32 (31)	40 (38)	30 (31)
Race, n (%)			
Caucasian	82 (80)	79 (76)	83 (85)
Black	20 (19)	23 (22)	14 (14)
Other	1 (1)	2 (2)	1 (1)

Source: Table 1 from Mr. Petullo's review

Baseline disease characteristics were relatively balanced across treatment groups, as summarized in the table below.

Table 3. Summary of Baseline Characteristics

Variable Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98	Total N=305
Baseline WOMAC Pain Subscale score				
N	103	104	98	305
Mean (SD)	75.27 (17.27)	73.42 (15.22)	76.18 (14.15)	74.93 (15.61)
Median	79.00	74.70	77.50	76.80
Minimum[a], maximum	(14.2, 98.2)	(11.2, 99.6)	(40.2, 100.0)	(11.2, 100.0)
Baseline Total (Composite) WOMAC score				
N	100	100	94	294
Mean (SD)	71.60 (17.24)	70.26 (15.69)	72.83 (15.87)	71.54 (16.27)
Median	74.00	70.80	75.45	73.60
Minimum, maximum	(16.2, 98.1)	(39.4, 99.1)	(33.4, 100.0)	(16.2, 100.0)
Missing	3	4	4	11
Baseline Pain Intensity VAS score				
N	100	100	94	294
Mean (SD)	71.5 (18.82)	69.6 (19.99)	71.8 (19.33)	71.0 (19.35)
Median	74.5	73.5	74.5	74.0
Minimum, maximum	(18, 97)	(4, 100)	(5, 100)	(4, 100)
Missing	3	4	4	11

Source: Section 14.1, Table 14.1.2

Source: Table 7 from Dr. Galati's review

Results:

Mr. Petullo noted in his review that:

> The pre-specified primary efficacy endpoint was defined as the mean change from baseline in the WOMAC pain subscale score at Week 12 or early termination. The WOMAC pain subscale score consists of five questions regarding pain during walking, using the stairs, in bed, sitting or lying, and standing. Each question is answered on a 100 mm VAS scale with 0 being no pain and 100 the worst possible pain. An overall score was derived by averaging the five scores.

The results for the primary efficacy analysis demonstrated a significant difference between the Zorvolex 35 mg TID group and placebo. Although the results for the Zorvolex 35 mg BID group demonstrated a trend towards a treatment effect, this finding did not reach statistical significance. Mr. Petullo confirmed the Applicant's findings for the primary efficacy endpoint by comparing the average change from baseline at Week 12 in the WOMAC pain subscale for the Zorvolex 35 mg TID and BID groups to placebo, and those results, utilizing Mr. Petullo's approach for discontinued subjects described above, are summarized in the table below. All of Mr. Petullo's analyses in the table below account for missing pain scores and use of rescue medication. Mr. Petullo notes that:

> In my analysis, if a subject used rescue medication within 12 hours of [a] scheduled study visit, I randomly assigned a score from the distribution of baseline scores and used this in my analysis.

Table 4. Summary of Results from Statistical Review Team's Analysis of the Primary Endpoint

Analysis	Imputation	Mean change from baseline pain at Week 12 (stdev)		
		placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
MMRM	none	35.0 (2.9)	41.7(2.8)	46.6 (3.0)*
ANCOVA	BOCF	28.9 (3.2)	36.4 (3.2)	39.3 (3.4)*
ANCOVA	BOCF/LOCF	30.4 (3.2)	38.3 (3.2)	40.1 (3.4)*
ANCOVA	return to BL	28.7 (3.2)	36.4 (3.3)	40.3 (3.5)*

* p-value for comparison to placebo < 0.05

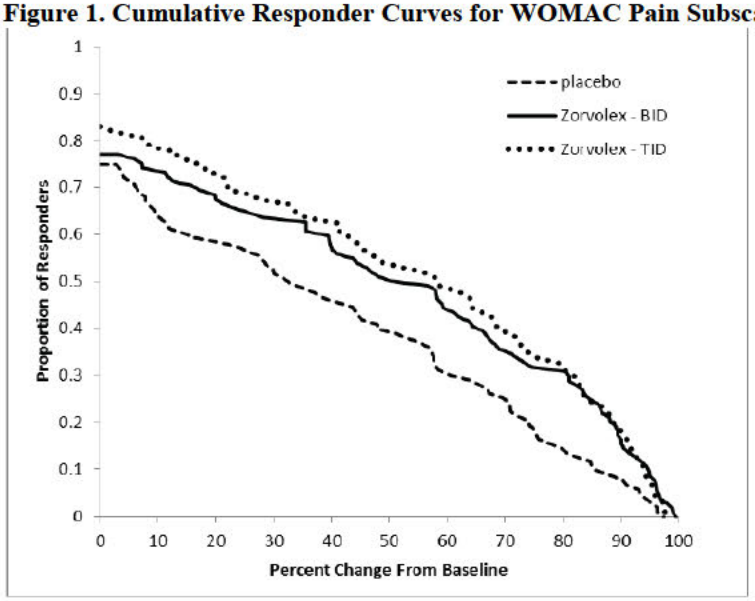
Source: Table 3 from Mr. Petullo's review

Both the Applicant's results and Mr. Petullo's results from multiple analyses on the primary endpoint consistently demonstrate a statistically significant difference between the Zorvolex 35 mg TID group and placebo in favor of a treatment effect. Although subjects treated with Zorvolex 35 mg BID had numerically larger reductions in the WOMAC pain subscale from baseline compared to placebo, this finding consistently did not reach statistical significance.

Mr. Petullo evaluated the amount of rescue medication use within 12 hours of a scheduled study visit and the amount of missing data (i.e., due to discontinuations) and assessed their impact on the primary analysis. Both rescue medication use within 12 hours of a scheduled study visit and the amount of missing data were low and regardless of how Mr. Petullo handled missing data in his analysis (see table above), there was a statistically significant treatment effect in favor of the Zorvolex 35 mg TID group but not for the BID group. I concur with Mr. Petullo's assessment that neither the use of rescue nor the amount of missing data influenced the primary analysis.

Mr. Petullo also examined cumulative responder curves for each treatment group; he considered subjects who did not complete the study as non-responders for this analysis. As demonstrated in the figure below and as noted in Mr. Petullo's review, there was clear separation between both doses of Zorvolex and placebo at all response levels.

Figure 1. Cumulative Responder Curves for WOMAC Pain Subscale Score



Source: Figure 1 from Mr. Petullo's review

The secondary and post-hoc exploratory efficacy analyses are supportive of a treatment effect in favor of Zorvolex and that, on balance, the 35 mg TID dosing regimen is the only efficacious dosing regimen. Refer to Mr. Petullo's and Dr. Galati's reviews for detailed results on these analyses.

Mr. Petullo concluded that:

> In Study DIC3-08-05, the efficacy of Zorvolex 35 mg TID was demonstrated in treating chronic pain associated with OA of the hip or knee as indicated by the significance of the pre-specified primary endpoint and was supported by the significance of various secondary endpoints. There were no concerns regarding the analysis populations, statistical analyses, imputation of missing data, and use of rescue medication that could not be addressed.

Dr. Galati also concluded that efficacy was demonstrated for the Zorvolex 35 mg TID group in the management of OA pain, but that efficacy was not demonstrated for the Zorvolex 35 mg BID group. I concur with both Mr. Petullo's and Dr. Galati's conclusions.

The Division provided (b) (4) , and the Applicant provided a response on July 28, 2014. That response was (b) (4) and consisted of a post-hoc primary MMRM analysis that included efficacy assessments that were considered missing and not included in the Applicant's prespecified primary MMRM analysis due to rescue medication use within 12 hours of the efficacy assessment. The Applicant's post-hoc primary MMRM analysis demonstrated statistical significance for (b) (4) TID dosing regimen compared to placebo. Additionally, the Applicant identified a placebo responder (Week 2 WOMAC pain subscale score of -14.6, Week 6 score of -0.4, and Week 12 score of

-85.6; all relative to baseline) and performed a re-analysis of the primary MMRM analysis changing the Week 12 pain subscale score for this subject to the Week 6 score (similar to Last Observation Carried Forward). The Applicant was able to demonstrate a statistically significant treatment effect (b) (4) However, these analyses pose several problems. First, both analyses were conducted post-hoc and were not prespecified. Secondly, it is not appropriate to discount a placebo subject just because that subject had a response. Furthermore, the re-analysis of the primary MMRM analysis that included the pain scores for subjects who took rescue medication 12 hours prior to a scheduled study visit is not acceptable because those scores likely reflect a relatively better score after rescue medication use rather than the relatively worse score that prompted the rescue medication use. Additionally, both post-hoc analyses utilized an MMRM approach in which missing data was assumed to be missing at random. Therefore, patients who discontinued due to an adverse event may be assigned a treatment benefit, whereas, these patients should be considered treatment failures. The drawbacks of the Applicant's re-analyses, in combination with the fact that (b) (4) on the Applicant's prespecified primary analysis nor was it demonstrated in Mr. Petullo's confirmatory primary analysis or the multiple sensitivity analyses that Mr. Petullo conducted to account for missing data (see Table 4 above), lead me to continue to conclude that efficacy was not demonstrated (b) (4).

The Applicant has not evaluated comparative efficacy between the reference drug, Cataflam, and Zorvolex in any of their clinical development programs (i.e., acute pain, OA pain) to date. As such, they have not provided any support for the assertion that this reformulation of diclofenac can provide comparable pain relief to Cataflam tablets at an approximately 20% lower dose.

It should be noted that in order to have satisfied the requirements for an indication of the management of the signs and symptoms of OA, the Applicant would have had to demonstrate a treatment effect on pain of OA (i.e., change from baseline in the WOMAC pain subscale), function in OA (i.e., change from baseline in the WOMAC function subscale), and Patient Global Impression of Change (PGIC) with appropriate statistical methods to address multiple comparisons on these endpoints. Although the Applicant did evaluate PGIC and change from baseline in the WOMAC function subscale among the treatment groups, these analyses were performed as secondary and post-hoc analyses, respectively, without appropriate statistical measures to control for multiplicity. Therefore, as the Applicant demonstrated efficacy on one primary endpoint (i.e., change from baseline in WOMAC pain subscale), the most appropriate indication is management of the pain of OA. This issue was discussed with the Applicant during the SPA (see Section 2, Background above).

8. Safety

The safety portion of this NDA review was conducted by Steven Galati, MD, with secondary concurrence by me. Zorvolex 35 mg capsules dosed BID and TID appear to be relatively well-tolerated among patients in the OA clinical development program. No new or unexpected safety signals were observed for Zorvolex, as compared to what is already known about diclofenac. The following is a summary of Dr. Galati's review.

The safety evaluation of Zorvolex in patients with OA pain primarily consisted of data from the pivotal Phase 3 clinical trial in OA (DIC3-08-05) and a 52-week open-label safety study in patients with OA of the hip or knee (DIC3-08-06). Patients in the open-label safety study could have continued into this study from the pivotal Phase 3 study or they could have been recruited independently. All subjects in this study began treatment with Zorvolex 35 mg BID. After four days, the dosing regimen could be titrated up to 35 mg TID, and the dosing regimen could be further titrated up or down between the BID and TID dosing regimens over the course of the study.

The pivotal Phase 3 clinical trial consisted of 305 subjects who were randomized to three treatment groups and received study medication, and the open-label safety study consisted of 601 subjects treated with Zorvolex 35 mg BID or TID. In total, 705 unique study subjects were treated with Zorvolex 35 mg BID or TID. As requested at the Pre-NDA meeting, the Applicant reported long-term exposure and safety data for the TID dosing regimen as this is the efficacious dosing regimen. A total of 161 subjects were exposed to the TID dosing regimen for 6 months or longer (426 subjects for the combined BID and TID dosing regimens) and 83 subjects were exposed to the TID dosing regimen for 11 months or longer (373 subjects for the combined BID and TID dosing regimens).[2] Although the Applicant's safety database did not technically satisfy the Division's requirements specifically for the efficacious dosing regimen, Dr. Galati concluded that the submitted safety database was acceptable for the following reasons: 1) the known safety profile of diclofenac, 2) the exposure for the combined BID and TID dosing regimens exceeds the safety database requirements, and 3) the Cmax and systemic exposure for the proposed product is lower than the reference product (refer to my CDTL memo for the acute pain indication dated September 30, 2013). Additionally, the safety review did not reveal any significant safety concerns for the TID dosing regimen compared to the BID dosing regimen other than what would be expected for an NSAID. In fact, patients who titrated to the TID dosing regimen in the open-label study did not often titrate back down to the BID dosing regimen (Refer to Table 27 in Dr. Galati's review for more details). Therefore, I concur with Dr. Galati's conclusion that the exposure to Zorvolex is adequate to assess safety for the intended OA population.

There were no deaths reported in studies DIC3-08-05 or DIC3-08-06.

[2] Two-hundred sixty-eight (268) subjects were exposed to the combined BID and TID dosing regimens for 12 months or longer; however, only 4 subjects were exposed to the TID dosing regimen for 12 months or longer because of the study design (i.e., subjects were not able to titrate up to the TID dosing regimen until after the first 4 days of the 52-week trial).

Nonfatal serious adverse events (SAEs) were reported in 3 subjects in the Zorvolex 35 mg BID group, 4 subjects in the Zorvolex 35 mg TID group, and 2 subjects in the placebo group in the pivotal Phase 3 trial. A total of 48 SAEs were reported in the open-label safety study (29 in the BID group and 19 in the TID group) in 42 subjects. Dr. Galati reviewed the case report forms and narratives for the SAEs in both studies and found no new or increased safety signals for Zorvolex beyond what is already known for diclofenac, and I concur with his assessment.

In the pivotal Phase 3 clinical trial, 47 subjects discontinued early. Two subjects in the Zorvolex 35 mg BID group and six subjects in the placebo group withdrew due to lack of efficacy, whereas none did in the Zorvolex 35 mg TID group. Twenty-five subjects (8.2%) withdrew from the pivotal Phase 3 trial due to an adverse event with four (3.9%) coming from the placebo group, nine (8.7%) from the BID group, and 12 (12.2%) from the TID group. A total of 97 subjects (16.1%) discontinued due to an adverse event in the open-label safety study, consisting of 61 (10.1%) in the BID group and 35 (11.6%) in the TID group. Dr. Galati reviewed the case report forms and narratives for subjects who discontinued due to an adverse event and noted that, for the pivotal Phase 3 trial, "although there is a trend towards increased number of withdrawals due to a[n] [adverse event] for the [Zorvolex] groups, with a slight increase in the TID group, the overall number of withdrawals were relatively small and represent known adverse events associated with diclofenac." For both the pivotal Phase 3 trial and the open-label safety study, Dr. Galati's review of the case report forms and narratives for subjects who discontinued due to an adverse event did not reveal any new safety signals for Zorvolex beyond what is already known for diclofenac. However, one subject discontinued due to elevated liver function tests that met criteria for Hy's law (i.e., ALT values $\geq$3X ULN, AST values $\geq$3X ULN, and bilirubin values $\geq$2X ULN).

This subject developed elevated liver function tests meeting criteria for Hy's law while being treated with Zorvolex 35 mg TID for approximately 5.5 months. The case narrative did not report any other symptoms associated with this event. Study medication was discontinued, and the subject's liver function tests returned to normal. Although this represents a concerning finding in a clinical study, NSAIDs, including diclofenac products, are labeled with a warning for severe, and possibly fatal, hepatotoxicity. The hepatotoxic adverse reaction that occurred in the context of the open-label safety study is within the realm of what is already described in NSAID labeling (including Zorvolex), and the reaction did not occur at a frequency that requires additional labeling or regulatory action.

In the pivotal Phase 3 clinical trial, 155 subjects reported at least one treatment-emergent adverse event (TEAE) with the majority of events being of mild to moderate intensity. Severe TEAEs were reported for 11 subjects (3.6%): six subjects (5.8%) in the Zorvolex 35 mg TID group, two subjects (2.0%) in the Zorvolex 35 mg BID group, and three subjects (2.9%) in the placebo group. A summary of TEAEs experienced by at least 2% of Zorvolex-treated subjects and occurring at a greater frequency than placebo for the pivotal Phase 3 trial is reviewed in the table below.

Table 5. Summary of TEAEs Occurring in at Least 2.0% of Zorvolex-treated Subjects and at Greater Frequency than Placebo in Trial DIC3-08-05

Preferred Term, n (%)	Placebo n=103	Diclofenac 35 mg bid n=104	Diclofenac 35 mg tid n=98	Combined diclofenac n =202
Subjects with ≥1 TEAE	46 (45)	50 (48)	59 (60)	109(54)
Nausea	2 (2)	5 (5)	9 (9)	14 (7)
Diarrhea	3 (3)	5 (5)	7 (7)	12 (6)
Headache	3 (3)	2 (2)	6 (6)	8 (4)
Abdominal pain upper	1 (1)	3 (3)	4 (4)	6 (3)
Sinusitis	1 (1)	2 (2)	3 (3)	5 (2.5)
Vomiting	1 (1)	2 (2)	3 (3)	5 (2.5)
ALT increase	0	1 (1)	3 (3)	5 (2.5)
Creatinine increase	0	1 (1)	3 (3)	4 (2)
Dyspepsia	1 (1)	1 (1)	3 (3)	4 (2)
Flatulence	0	2 (2)	2 (2)	4 (2)
Hypertension	1 (1)	3 (3)	1 (1)	4 (2)
AST increase	0	0	2 (2)	2 (1)

Source: Table 35 from Dr. Galati's review

TEAEs for the open-label safety study are summarized in the table below.

Table 6. Summary of TEAEs Occurring in >2% of the Combined Zorvolex Capsules 35 mg Group in Study DIC3-08-06

Preferred Term	Zorvolex Capsules 35 mg bid N=601 n (%)	Zorvolex Capsules 35 mg tid N=302 n (%)	Zorvolex Capsules 35 mg Combined N=601 n (%)
Any TEAE[a]	340 (56.6)	186 (61.6)	451 (75.0)
Upper respiratory tract infection	27 (4.5)	21 (7.0)	47 (7.8)
Headache	36 (6.0)	11 (3.6)	46 (7.7)
Urinary tract infection	34 (5.7)	10 (3.3)	44 (7.3)
Diarrhoea	24 (4.0)	14 (4.6)	37 (6.2)
Nasopharyngitis	24 (4.0)	11 (3.6)	34 (5.7)
Nausea	22 (3.7)	11 (3.6)	33 (5.5)
Constipation	22 (3.7)	6 (2.0)	29 (4.8)
Sinusitis	22 (3.7)	7 (2.3)	29 (4.8)
Osteoarthritis	16 (2.7)	11 (3.6)	27 (4.5)
Cough	14 (2.3)	9 (3.0)	23 (3.8)
Alanine aminotransferase increased	13 (2.2)	8 (2.6)	21 (3.5)
Back pain	11 (1.8)	9 (3.0)	20 (3.3)
Dyspepsia	12 (2.0)	7 (2.3)	19 (3.2)
Procedural pain	10 (1.7)	8 (2.6)	18 (3.0)
Bronchitis	12 (2.0)	5 (1.7)	17 (2.8)
Hypertension	9 (1.5)	8 (2.6)	17 (2.8)
Abdominal pain upper	11 (1.8)	5 (1.7)	16 (2.7)
Influenza	10 (1.7)	6 (2.0)	16 (2.7)
Arthralgia	7 (1.2)	8 (2.6)	15 (2.5)
Contusion	10 (1.7)	6 (2.0)	15 (2.5)
Vomiting	6 (1.0)	9 (3.0)	15 (2.5)
Abdominal discomfort	8 (1.3)	6 (2.0)	14 (2.3)
Aspartate aminotransferase increased	7 (1.2)	7 (2.3)	14 (2.3)
Dizziness	10 (1.7)	4 (1.3)	14 (2.3)
Fall	11 (1.8)	3 (1.0)	14 (2.3)
Abdominal pain	9 (1.5)	4 (1.3)	13 (2.2)

Source: Applicant's Summary of Clinical Safety, Table 2.7.4.3.2.1-1

Dr. Galati's review of TEAEs for the pivotal Phase 3 clinical trial and the open-label safety study did not reveal any additional safety information that would alter the risk-benefit profile of Zorvolex, or diclofenac in general.

The review of safety demonstrated that Zorvolex 35 mg given BID or TID appears well-tolerated by patients with OA pain and that there were no significant safety concerns for the TID dosing regimen as compared to the BID dosing regimen beyond what is expected for an NSAID. Dr. Galati concluded that no new or unexpected safety signals were detected for Zorvolex, or diclofenac in general, during this review, and I concur with his conclusion.

The Applicant has not evaluated comparative safety between the reference drug, Cataflam, and Zorvolex in any of their clinical development programs (i.e., acute pain, OA pain) to date. As such, they have not provided any support for the assertion that this reformulation of diclofenac at a lower dose may have the potential for an improved safety profile compared to Cataflam.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

No studies have been carried out in pediatric patients. The Applicant submitted a pediatric plan that includes a request for full waiver of the pediatric study requirements under the Pediatric Research Equity Act (PREA) given that studies would be highly impractical or impossible due to the extremely limited incidence of OA in the pediatric population. The Division concurs with granting a full waiver for this indication for the reason stated. The pediatric plan was discussed at a meeting of the Pediatric Research Committee (PeRC) on July 2, 2014, and the PeRC agreed with granting a full waiver.

11. Other Relevant Regulatory Issues

Inspections by the Office of Scientific Investigations (OSI)
Cynthia F. Kleppinger, MD, completed the Clinical Inspection Summary for this sNDA, with secondary concurrence by Janice Pohlman, MD, MPH, and Kassa Ayalew, MD, MPH.

According to Dr. Kleppinger's review, the overall assessment of the inspectional findings was that:

> In general, based on the inspection of the two clinical study sites, the inspectional findings support validity of data at their sites and as reported by the sponsor under this supplemental NDA.
>
> Observations for Dr. Kivitz are based on the review of the draft Establishment Inspection Report (EIR) and communications from the field investigator. Observations noted for Dr. Thomas are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

The following two study sites for DIC3-08-05, the pivotal clinical trial, were inspected:

Name of CI/ Site #	**Protocol DIC3-08-05 # of Subjects Randomized**	**Inspection Date**	**Preliminary Classification**
Alan J. Kivitz, MD, CPI Site #101	17	June 2-4, 2014	NAI
Haydn Mikel Thomas, MD Site #106	27	April 23-25, 2014	NAI

Key to Classification
NAI = No deviation from regulations
Source: Dr. Kleppinger's review, p 2.

Financial Disclosures
The Applicant submitted certification that no investigators have any financial interests or arrangements to disclose.

505(b)(2) Committee
This application was presented at a 505(b)(2) clearance meeting on July 7, 2014, and it was cleared for action from their perspective.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed changes to the insert labeling, and DMEPA has no additional comments or edits at this time. Additionally, the Office of Prescription Drug Promotion (OPDP) evaluated the proposed labeling and had comments as detailed in their consult response dated July 17, 2014.

Labeling is ongoing at the time of this writing.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval of the Zorvolex 35 mg TID dosing regimen for management of OA pain

- Risk Benefit Assessment

The Applicant developed Zorvolex capsules as a new formulation of diclofenac with reduced particle size to, according to the Applicant, promote the dissolution and absorption

of diclofenac. The Applicant further purported that the improved dissolution properties of Zorvolex are associated with rapid absorption resulting in comparable pain relief to Cataflam tablets at an approximately 20% lower dose and that the lower dose may have the potential for an improved safety profile compared to Cataflam. Zorvolex capsules (18 mg and 35 mg) were recently approved on October 18, 2013, for the treatment of mild to moderate acute pain. In the current application for Zorvolex capsules 35 mg for the management of OA pain, as was the case in the previous application for acute pain, the Applicant has not provided any evidence comparing Zorvolex to Cataflam upon which to make any comparative safety or efficacy claims or to substantiate their rationale for developing this drug product.

Nevertheless, the Applicant did demonstrate evidence of efficacy for Zorvolex 35 mg capsules dosed TID for the management of OA pain in one Phase 3, randomized, double-blind, placebo-controlled, parallel-group clinical trial in adult patients with osteoarthritis of the hip or knee, on the primary efficacy endpoint, change from baseline at Week 12 in the WOMAC pain subscale. Although the results demonstrated a trend towards a treatment effect for the (b) (4), the finding consistently did not reach statistical significance for the primary efficacy endpoint, including multiple sensitivity analyses to account for missing data. The safety review demonstrated that Zorvolex 35 mg given BID or TID appears well-tolerated by patients with OA pain and that no new or unexpected safety signals were detected for Zorvolex or diclofenac in general. The safety review also demonstrated that there were not any significant safety concerns for the TID dosing regimen as compared to the BID dosing regimen beyond what would be expected for an NSAID. As the proposed product does not represent a significantly new treatment option for OA pain, I do not believe (b) (4) I conclude that the results of the clinical studies in this application, in combination with the Agency's previous findings of safety and efficacy for the reference product (i.e., Cataflam), are acceptable to satisfy the regulatory requirements for approval of the TID dosing regimen of this product, (b) (4), for the management of OA pain.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  None

- Recommended Comments to Applicant

  None

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/s/

JOSHUA M LLOYD
08/07/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	204592
Priority or Standard	Standard
Submit Date(s)	October 31, 2013
Received Date(s)	October 31, 2013
PDUFA Goal Date	August 31, 2014
Division / Office	DAAAP/ODE II
Reviewer Name(s)	Steven Galati MD
Review Completion Date	July 22, 2014
Established Name	Diclofenac
(Proposed) Trade Name	Zorvolex
Therapeutic Class	NSAID
Applicant	Iroko Pharmaceuticals
Formulation(s)	Capsule
Dosing Regimen	35 mg taken TID
Indication(s)	Osteoarthritis pain
Intended Population(s)	Patients with osteoarthritis pain

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with revisions to the proposed label.

1.2 Risk Benefit Assessment

The Applicant submitted the results of a pivotal, Phase 3 trial, as well as a 52-week open-label safety study, for the treatment of osteoarthritis pain. This is a supplemental application to the approved Zorvolex product (10/19/2013) indicated for the treatment of acute mild to moderate pain. I have determined that the pivotal trial was designed and conducted in a reasonably adequate and well-controlled fashion that is sufficient to rely upon for a determination of efficacy and safety. Also, the open-label safety study adequately addressed the exposure and safety requirements set forth by the Division. The data reviewed, in the pivotal controlled clinical trial, in patients with osteoarthritis pain of the knee or hip, support the effectiveness of 35 mg dosed three times a day (TID) with diclofenac acid capsules for the treatment of osteoarthritis pain in this population as evidenced by the statistical significance of the primary endpoint compared to placebo and the clinically meaningful benefit of this finding. The safety data did not demonstrate any new safety signal beyond what is already known for diclofenac. The safety profile for the intended patient population is acceptable.

Benefits:

- Evidence of effectiveness of diclofenac 35 mg TID was established in a single, pivotal, placebo-controlled, 12-week trial using the primary endpoint, the Western Ontario and MacMaster University Osteoarthritis Index Pain Subscale (WOMAC Pain Subscale), a validated questionnaire used to quantify the amount of pain experienced by patients with osteoarthritis
- The primary analysis was further confirmed in a multiple sensitivity analyses on this endpoint (see Section 6 for more details)
- The primary efficacy analysis is further supported by results in favor of diclofenac on various secondary endpoints
- Diclofenac is a well-established analgesic and this dosage form offers an additional treatment option for patients with osteoarthritis pain

Risks:

- No new safety signal was identified in review of this application

Overall, the risk-benefit profile of diclofenac acid capsules in this population is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in the review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

No additional pediatric studies are required. The Division granted a full waiver because the disease/condition does not occur in pediatric patients. In a meeting on 7/2/14, the pediatric research committee (PeRC) agreed with the Division in our recommendation of granting a full waiver.

2 Introduction and Regulatory Background

2.1 Product Information

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Diclofenac is a potent inhibitor of both COX-1 and COX-2. The efficacy of diclofenac is believed to be associated with the inhibition of COX-2 while the adverse effects of diclofenac are probably related to inhibition of COX-1, which causes a decrease in prostaglandin synthesis. The Applicant developed a new formulation (as an acid form called Zorvolex) of diclofenac capsules in 18mg and 35mg doses to be taken three times per day. This new formulation was studied in a single, pivotal trial in patients with acute pain after bunionectomy and approved for the acute pain indication on 10/18/13. The Applicant has submitted additional studies, a 12-week efficacy study and 52-week open-label safety study, for the indication of treatment of osteoarthritis pain.

Zorvolex (diclofenac acid capsules) are immediate release capsules with the indication for the treatment of mild to moderate pain in adults. The Applicant's rationale for developing Zorvolex is that they purport their technology significantly reduces particle size promoting the dissolution and absorption of diclofenac. The Applicant believes the improved dissolution properties of Zorvolex 35 mg capsules are associated with rapid absorption resulting in comparable pain relief to Cataflam tablets at a 20% lower dose of diclofenac than Cataflam 50 mg tablets. They also purport that the lower dose may have the potential for an improved safety profile compared with Cataflam 50 mg tablets. Although, the Applicant has not provided any data to support this rationale.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alternative treatment options include other prescription strength NSAIDs and acetaminophen.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple approved drug products containing the active ingredient diclofenac are available and marketed in the United States as a treatment for multiple indications (Table 1).

Table 1: Brand Name Diclofenac Products and Indications

Drug Product Name	NDA	Approval Date	Dose Form	Indication
Zipsor	22202	06/16/2009	Capsule	Relief of mild to moderate pain
Pennsaid	20947	11/04/2009	Lotion	Treatment of signs and symptoms of osteoarthritis
Diclofenac Patch	21234	01/31/2007	Patch	Treatment of pain in minor sports injuries
Voltaren Gel	22122	10/17/2007	Gel	Treatment of osteoarthritis of joints amenable to superficial treatment such as the hands and knees
Voltaren	19201	07/28/1988	Tablet	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis Acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis
Cataflam	20142	11/24/1993	Tablet	Treatment of primary dysmenorrhea Relief of mild to moderate pain; signs and symptoms of osteoarthritis and rheumatoid arthritis
Voltaren XR	20254	03/8/1996	Tablet	Treatment of rheumatoid arthritis and osteoarthritis
Zorvolex	204592	10/18/2013	Capsule	Treatment of acute pain

2.4 Important Safety Issues With Consideration to Related Drugs

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patient's with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. NSAIDs are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAID's cause an increased risk of serious gastrointestinal adverse events

including bleeding, ulceration, hepatic injury and perforation of the stomach or intestines, which can be fatal.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Multiple products containing the active ingredient diclofenac have previously been approved in the United States for a number of indications, as listed above (Table 1). The application for Zorvolex (diclofenac acid) Capsules was originally submitted and filed as a 505(b)(2) NDA relying upon the Agency's previous findings of safety and efficacy for Cataflam (020142). For key regulatory events related to Zorvolex for acute pain please see my review from 9/17/2013.

Key regulatory activity for this supplemental application related to this NDA is noted in Table 2 that follows.

Table 2: Key Regulatory History for sNDA 204592

Date	Meeting/ Submission Type	Comments
7/14/11	Special Protocol Assessment- No agreement	• Study design appropriate for treatment of osteoarthritis pain • Primary endpoint of WOMAC pain subscale is acceptable • Implied safety claims will not be permitted in labeling or promotional materials without demonstration of improved outcomes in a dedicated safety study
5/23/13	Type B p-NDA meeting	• Efficacy trial DIC3-08-05 appears adequate for filing • Safety trial DIC3-08-06 must analyze safety based on dose regimen (BID vs. TID) • No additional PK studies required • Safety analyses should be of the pooled trials as well as individual reports

2.6 Other Relevant Background Information

For additional background information refer to the NDA review for Zorvolex for the treatment of acute pain from 9/17/2013.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidance for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were not in Study Data Tabulation Model (SDTM) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

The Office of Scientific Investigations (OSI) conducted routine inspection of two domestic clinical investigator sites in support of this NDA (Table 3). Neither site was issued a Form FDA 483; the classifications of both inspections were NAI (No Action Indicated). Dr. Kleppinger determined the inspectional findings support validity of data at their sites and as reported by the Applicant under this sNDA.

Table 3: OSI Evaluation of Clinical Inspections

Name of CI/ Site #	Protocol DIC3-08-05 # of Subjects Randomized	Inspection Date	Preliminary Classification
Alan J. Kivitz, MD, CPI Site #101	17	June 2-4, 2014	NAI
Haydn Mikel Thomas, MD Site #106	27	April 23-25, 2014	NAI

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations

Source: Dr. Cynthia F. Kleppinger's clinical inspection summary, p.2

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", attached with a list of investigators at 40 clinical sites, certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure). I counted a total of 201 investigators at these sites. None of the investigators had financial interests or arrangements to disclose, thus the possibility of bias in the results based on financial interests is unlikely.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No clinically relevant data was submitted to or reviewed by the chemistry manufacturing and controls, clinical microbiology, clinical pharmacology, preclinical and pharmacology/toxicology review disciplines. Therefore, sections 4.1, 4.2, 4.3, and 4.4 were deleted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials conducted in support of this supplemental sNDA for diclofenac capsules are listed in below (Table 4).

Table 4: Clinical Trials Submitted in Support of this Application

Clinical Trial	Population	Number of Subjects	Relevance
Clinical Trials Contributing to Efficacy Review (Controlled Trials)			
DIC3-08-05	Osteoarthritis of the knee or hip	Zorvolex = 35 mg BID (n=104), 35 mg TID (n=98), Placebo = (n=103)	Contains efficacy data in osteoarthritis pain population
Clinical Trials Contributing to Safety Review			
DIC3-08-05	Osteoarthritis of the knee or hip	Zorvolex = 35 mg BID (n=104), 35 mg TID (n=98), Placebo = (n=103)	Contains safety data in osteoarthritis pain population
DIC3-08-06	Osteoarthritis of the knee or hip	Zorvolex = 602 subjects with ability to titrate dose between 35 mg BID and 35 mg TID	Contains safety data in osteoarthritis pain population

Source: Derived from Applicant's submission, sNDA 204592

5.2 Review Strategy

DIC3-08-05 (controlled trial) is the pivotal trial reviewed for efficacy and safety. DIC3-08-06 provided additional safety data on subjects who were exposed to diclofenac for longer periods of time as requested by the Division. The primary analyses of efficacy will rely only on trial DIC3-08-05, along with the Agency's previous findings of effectiveness for diclofenac [505(b)(2)]. The primary analyses of safety will rely only on DIC3-08-05 and DIC3-08-06, along with the Agency's previous findings of safety for diclofenac [505(b)(2)]. The design and results from the individual controlled trials submitted in support of efficacy in the indicated population are reviewed in Section 5.3, Discussion of Individual Studies/Clinical Trials. The primary efficacy analyses of trial DIC3-08-05 were confirmed by Mr. David Petullo, statistical reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

Trial DIC3-08-05

"A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, Parallel-Group, Efficacy and Safety Trial of Diclofenac Nanoformulation Capsules in Subjects with Osteoarthritis of the Knee or Hip"

Conducted from October 25, 2011 through March 28, 2012

Forty sites, all located in the United States

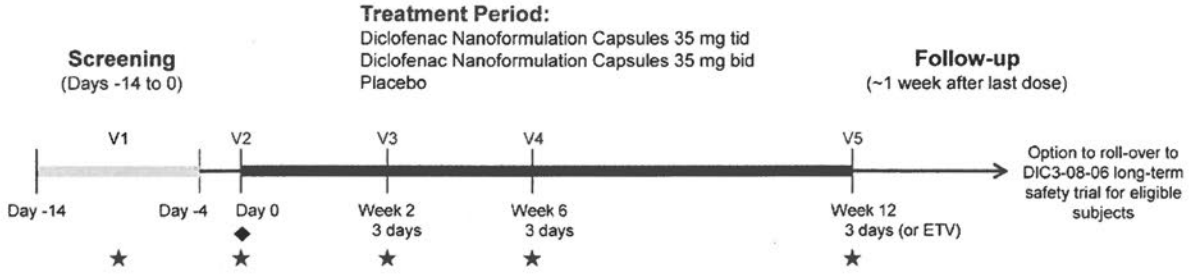
Protocol

Objective/Rationale
The primary objective is to evaluate the analgesic efficacy and safety of diclofenac capsules 35 mg administered BID and TID, compared with placebo, in subjects with osteoarthritis pain of the hip or knee.

Overall Design
This was to be a Phase 3, multicenter, randomized, double-blind, multiple-dose, fixed-dose, parallel-group, active- and placebo-controlled study to evaluate the safety and efficacy of 2 dosing regimens of diclofenac (35 mg BID and TID) in subjects with pain due to OA of the knee or hip. Subjects' maximum duration on trial drug was to be 12 weeks. Screening (Visit 1) was to be approximately 2 weeks before randomization. Screening procedures were to be completed prior to the baseline visit (Visit 2). There was to be a washout period equal to ≥5 half-lives of any pain medication after Visit 1 to induce an acceptable flare. At Visit 2, subjects who met trial entry criteria, and experienced an acceptable flare, were to be eligible. An acceptable flare was to be defined as Western Ontario and McMaster Universities OA Index (WOMAC) Pain Subscale score (Visual Analogue Scale [VAS]-normalized on a 0 to 100 mm scale) of ≥ 40 mm at Visit 2 and an increase of ≥ 15 mm between Visits 1 and 2. Subjects were to be randomized to 1 of 3 treatment groups (diclofenac 35 mg BID, TID or placebo) at Visit 2 and administered treatment in blinded, double-dummy blister-pack dosing cards. A total of 5 visits were to be included in the trial, including a follow-up visits (Visit 5) about 1 week after the final dose (Figure 1). Subjects were to be instructed to take the medication on an empty stomach

and return to the trial site for visits at Week 2 (Visit 3), Week 6 (Visit 4), and Week 12 (Visit 5) to be monitored for safety and to complete scheduled procedures and assessments of efficacy. Acetaminophen, up to 500 mg administered every 4 to 6 hours, was to be allowed as needed during the treatment period for rescue and prohibited within 12 hours before the trial visits 2-5. Safety was to be assessed by the incidence of treatment-emergent adverse events (TEAEs), physical examination findings, vital signs measurements, electrocardiograms (ECGs), and clinical laboratory evaluations. Eligible subjects who wished to continue treatment after the completion of DIC3-08-05 were allowed to roll-over to the long-term safety trial, DIC3-08-06.

Figure 1: Overall Design of DIC3-08-05



◆ = randomization; ★ = pain and safety assessment; V = Visit; ETV = End-of-treatment Visit

Source: Clinical study report DIC3-08-05, p.26

Treatment

Once the pain intensity entry criteria were to be met, subjects were to be randomly assigned to diclofenac capsules 35 mg TID; diclofenac 35 mg BID; or placebo. Subjects were to be administered trial drug on each dosing day at approximately 7:00 AM, 3:00 PM, 7:00 PM, and 11:00 PM with additional doses using a double-dummy technique. During the washout period, rescue medication (acetaminophen) was to be allowed (maximum of 3000 mg per day) with the exception that it was to be discouraged within 24 hours and prohibited within 12 hours before Visit 2 (day of randomization). During the treatment period, acetaminophen (up to 500 mg administered every 4 to 6 hours) was to be allowed as needed (maximum of 3000 mg per day). During the treatment period, acetaminophen was to be discouraged within 24 hours and prohibited within 12 hours before visits Visits 3, 4, and 5.

Population and Procedures

Inclusion/Exclusion Criteria

Enrollment was to be 305 subjects randomized into the trial to receive diclofenac 35 mg TID, diclofenac 35 mg BID or placebo.

Key Inclusion Criteria

- Male or female ≥ 40 years of age

- Primary diagnosis of Functional Class I to III OA of the hip or knee[1]
- Current chronic user of NSAIDs and/or acetaminophen for his/her OA pain[2]
- Discontinued all analgesic therapy at screening (except trial-specified rescue medication) and refrained from taking trial-specified rescue medication for 12 hours before baseline
- WOMAC Pain Subscale (VAS 0 to 100 mm) ≥ 40 mm at baseline and had ≥15 mm increase (OA pain flare) in the valid WOMAC Pain Subscale-normalized VAS score from screening at baseline[3]
- Body weight of ≥ 45 kg and a body mass index (BMI) no greater than 40 kg/m2
- If female and of childbearing potential, was nonlactating and nonpregnant (had negative pregnancy test results at screening [serum] and Baseline [urine])
- If female, was either not of childbearing potential (defined as postmenopausal for ≥ 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing medically acceptable methods of birth control[4] and agreed to continue with the regimen throughout the trial
- Was able to walk
- Able to provide informed consent to participate in the trial and able to understand the procedures and trial requirements and willing to comply[5]

Key Exclusion Criteria

- History of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any NSAIDs[6]
- Chronic use of opioid or opioid combination products to control OA pain
- Clinically significant unstable medical conditions[7]
- History or current diagnosis of a significant psychiatric disorder that, in the opinion of the investigator, would affect the subject's ability to comply with the trial
- Receiving systemic chemotherapy, had an active malignancy of any type, or had been diagnosed with cancer within 5 years (excluding squamous or basal cell carcinoma of the skin)
- Had known or suspected history of alcoholism or drug abuse or misuse within 2 years
- Had a history of a clinically significant (investigator opinion) GI event within 6 months before screening or had any history of peptic or gastric ulcers or GI bleeding
- Had a surgical or medical condition of the GI or renal system that might have significantly altered the absorption, distribution, or excretion of any drug substance
- Had a history of major surgery on the target hip or knee joint at any time or a history of minor surgery (arthroscopy) on the target hip or knee joint within 1 year

---

[1] In documented hip OA must have articular hip pain and Radiographic Severity Grade II to III (Kellgren-Lawrence). In documented knee OA must have knee pain and Radiographic Severity Grade II to III (Kellgren-Lawrence)and at least 1 of the following 3 criteria: 1) age greater than 50 years; 2) morning stiffness < 30 minutes in duration; 3) crepitus.

[2] Defined as a subject who had used these treatments for ≥ 20 days 30 days before screening

[3] Subject had to answer ≥ 4 of the 5 questions on the Pain Subscale to be valid score

[4] Hormonal methods for minimum of 1 cycle; total abstinence since the last menses; Intrauterine device; Double-barrier method

[5] IRB approved consent form

[6] Includes NSAID induced bronchospasm, allergy, or these reactions to any other drugs to be used in the study

[7] Cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject safety or impair results

- Was considered by the investigator to be an unsuitable candidate to receive the trial drug (e.g., risks described in Investigator's Brochure)
- Had received hyaluronic acid injections in the target joint in the 6 months before screening
- Had received systemic corticosteroids (either oral or parenteral) or lower-limb intra-articular corticosteroids within 3 months before screening
- Expected to use concurrent analgesic, anti-inflammatory therapy, including aspirin (allowed only if administered at a morning dose no greater than 325 mg daily
- Was currently receiving or expected to use anticoagulants
- Had been treated with agents that could affect the analgesic response (such as central alpha agents [clonidine and tizanidine], neuroleptic agents, and other antipsychotic agents) within 2 weeks before dosing
- Had started physical therapy within 4 weeks before screening [not excluded if had ≥ 4 weeks of physical therapy (allowing time to stabilize on treatment) and were planning to remain on a stable regimen throughout the treatment]
- Had a current medical or arthritic disease that could have confounded or interfered with the evaluation of efficacy (e.g., rheumatoid arthritis, septic arthritis, systemic lupus erythematosus)
- Was a candidate for imminent (i.e., during the 5 months after screening) joint replacement
- Had tested positive either on the urine drug screen or on the alcohol breathalyzer test
- Had a significant renal or hepatic disease, as indicated by clinical laboratory assessment[8]
- Significant difficulties swallowing capsules
- Previously participated in another clinical trial of diclofenac, or received any investigational drug or device or investigational therapy within 30 days

Procedures

The study was to consist of a Screening Phase (Visit 1), a Washout Period (about 1 week before randomization), Treatment Phase (Visits 2-5 within 12 week period) and a Follow-up visit (1 week after last dose taken). Eligible subjects were to complete all Screening procedures within 14 days before the Baseline visit (Visit 2). The medication was to be administered QID for 48 hours after the first dose, with a maximum of 4 doses (active and/or dummy) in a 24-hour period. A detailed review of the scheduled events is shown in Table 5. Rescue medication (acetaminophen up to 500 mg administered every 4 to 6 hours) was to be allowed as needed during the treatment period (maximum of 3000 mg per day). Acetaminophen was to be allowed (but discouraged) within 24 hours and prohibited within 12 hours before the following trial visits: 2, 3, 4, and 5.

Screening and Washout period (Visit 1 - approximately 2 weeks before randomization)

- Subjects were to have assessed or instructed to:
  - Sign informed consent
  - Discontinue taking all prohibited medications and pain medications (except trial-specified) during washout period – 5 half-lives of drug taken
  - Provide demographics
  - History and Physical examination
  - Vital signs[9]

[8] Results ≥ 3 times the upper limit of normal for any liver function test or creatinine ≥ 1.5 times the upper limit of normal or had any clinically significant laboratory finding at screening that in the investigator's opinion contraindicated trial participation

[9] Blood pressure, heart rate, respiratory rate, and oral body temperature

- Clinical laboratory tests (hematology, chemistry, urinalysis)
- Pregnancy test for female subjects of childbearing potential
- Urine drug screen and alcohol breathalyzer test
- Target joint radiographs
- WOMAC pain, stiffness, and function subscales
- Dispense rescue (relevant for washout period due to flare)
- Review procedures/schedule visit

Treatment Phase

- At Visit 2:
  - Randomized
  - Complete baseline efficacy and safety assessments
  - Administered first dose of trial drug and given supply
  - Given instructions for using the drugs
- Subjects were to return at Week 2 (Visit 3 [V3]), Week 6 (Visit 4 [V4]), and Week 12 (Visit 5 [V5]) to be monitored for safety and complete scheduled procedures and assessments of efficacy as detailed in Table 2.

Follow-up Visit

- Subjects were to follow-up 1 week after last dose

Table 5: Schedule of Events

	Screening		Treatment Period		Follow-up	
	V1 Screening Visit (Days -14 to -4)	V2 Baseline Day 0	V3 Week 2 ± 2 days	V4 Week 6 ± 3 days	V5 Week 12 ± 3 days (or ET)	About 1 week after last dose of trial drug
Written informed consent	X					
Inclusion/exclusion criteria	X	X[a]				
Demographics	X					
Medical history	X	X[a,b]				
Physical examination	X[c]	X[a]			X	
Vital signs[d]	X	X[a]	X	X	X	X
Height, weight, and BMI	X				X[e]	
12-lead electrocardiogram	X				X	
Clinical laboratory tests (hematology, chemistry, urinalysis)	X			X	X	
Pregnancy test for female subjects of childbearing potential[f]	X	X[a]				
Urine drug screen	X	X[a]				
Alcohol breathalyzer test	X	X[a]				
Target joint radiographs[g]	X					
WOMAC pain, stiffness, and function subscales	X[h]	X[h]	X	X	X	
Randomization		X[a]				
Pain intensity (VAS)[i]		X[j]	X[j]	X[j]	X[j]	
Subject Global Impression of Change					X	
Clinical Global Impression of Change					X	
Health Survey (SF-36v2™)		X[k]			X	
Dispense rescue/trial drug	X	X	X	X		

	Screening		Treatment Period		Follow-up	
	V1 Screening Visit (Days -14 to -4)	V2 Baseline Day 0	V3 Week 2 ± 2 days	V4 Week 6 ± 3 days	V5 Week 12 ± 3 days (or ET)	About 1 week after last dose of trial drug
Collect rescue/trial drug and perform accountability		X	X	X	X	
Concomitant medications	X	X[a]	X	X	X	X
Adverse events		X[a]	X	X	X	X
Review procedures/schedule visit	X	X	X	X	X	

Abbreviations: BMI = body mass index; ETV = early termination visit; SF-36v2™ = Short Form-36 Health Survey, Version 2; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities OA Index.

[a] Assessment was performed before the first dose of trial drug was administered.
[b] Medical history since Screening was updated.
[c] A complete physical examination (excluding the genitourinary examination) was performed at Screening. Subjects were asked to identify their most painful joint. To be eligible for trial participation, the subject's most painful joint had to have been the target joint (knee or hip). An abbreviated physical examination (excluding the genitourinary examination) assessing changes from the initial physical examination was performed at V2 and V5 or ETV (whichever occurred first).
[d] Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, were measured after the subject had been in a sitting position for 5 minutes.
[e] Only weight measurement was performed at V5.
[f] Serum pregnancy test at Screening and urine pregnancy test were performed at Day 0 (Baseline). Test results had to be negative for the subject to continue in the trial.
[g] The radiographs were used to determine the American College of Rheumatology criteria and Kellgren-Lawrence grade.
[h] At Screening, only the WOMAC Pain Subscale assessments were completed. At Baseline, the WOMAC Pain Subscale assessments was completed before randomization. Randomized subjects were administered the WOMAC (including the pain, stiffness, and function subscales).
[i] For the VAS pain intensity assessments, subjects were asked "How much pain do you have right now?"
[j] Assessment was performed at V2 after randomization but before trial drug was dispensed and at V3, V4, and V5 at approximately the same time relative to trial drug dosing, preferably at a constant 2 to 4 hours after the morning trial drug dose.
[k] Assessment was performed at V2 after randomization but before trial drug was dispensed.

Source: Applicant's Clinical Study Report DIC3-08-05, p. 33-34

Subject Withdrawal

Subjects were to be free to withdraw from participation in this study at any time, for any reason, and without prejudice. Subjects were to be discontinued from the study at any time, in the best interest of the subject, at the discretion of the investigator. If a subject was to be withdrawn before completing the study, the reason for withdrawal was to be entered on the appropriate case report form (CRF).

Subjects could also be withdrawn from the study for the following reasons:

- Adverse events
  - Any AE was to be followed to a satisfactory resolution until it became stable or was to be explained by another known cause(s)
- Lack of therapeutic effect
- Intercurrent illness
- Noncompliance with procedures

Evaluations/Endpoints

Subjects were to complete the WOMAC pain, stiffness, and function subscales at screening, baseline and every visit during treatment. The WOMAC Pain Subscale score consists of the mean of the sum of the VAS scores from the 5 Pain Subscale questions on a 0 to 100 mm scale. Pain intensity was to be assessed at baseline and all visits during treatment using a VAS scale. The VAS is a horizontal line 100 mm in length with "No Pain" as the left anchor (0 mm) and "Worst Possible Pain" as the right anchor (100 mm). The subjects were to asked "How much pain do you have right now?" at randomization and at Visits 3, 4 and 5 at the same each visit (about 2-4 hours after morning dose).

The pre-specified primary efficacy variable was to be the mean change from Baseline in the WOMAC Pain Subscale score (difference between Baseline score and the Week 12 [V5]). The Division had previously agreed with the chosen primary endpoint (special protocol assessment 7/14/11). No secondary efficacy variables were identified as key.

Secondary efficacy variables identified in the protocol included:

- Mean change from Baseline in the WOMAC Pain Subscale score (difference between Baseline score and each scheduled visit score for Week 2 [V3] and Week 6 [V4])
- Mean change from Baseline in the WOMAC Pain Subscale score (difference between Baseline score and the average over the 12-week period)
- Mean change from Baseline in the Total WOMAC score (the Composite score was to be obtained by normalizing the sum of the VAS scores from the questions in the pain, stiffness, and physical function subscales; the mean change from Baseline was to be computed as the difference between Baseline score and the average over the 12-week period)
- VAS pain intensity (difference between Baseline score and the average over the 12-week period)
- PGIC and CGIC scores at Week 12 (V5)
- Amount of rescue medication taken by each subject
- Cumulative discontinuations due to lack of efficacy at Week 12
- Mean changes from Baseline in the 2 summary scores (mental component score [MCS] and physical component score [PCS]) of the SF-36v2™ (difference between Baseline score and Week 12 visit score)
- Responder rates for subjects with ≥ 30% and for subjects with ≥ 50% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively), as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS pain intensity scores
- Continuous responder rates for subjects who achieved a reduction in pain, evaluated at a continuous cutoff ranging from 0% to 100% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively) as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS pain intensity scores. (NOTE: all subjects who withdrew early from the trial were considered nonresponders)

Safety Assessments:

- Measure treatment-emergent adverse events (TEAEs), physical examination findings, vital signs measurements, electrocardiograms (ECGs), and clinical laboratory evaluations

Statistical Plan

The primary efficacy variable was to be the mean change from Baseline in the WOMAC Pain Subscale score (difference between Baseline score and the Week 12 [V5]). The intent-to-treat (ITT) population was to consist of all subjects who received at least 1 dose of study drug. The ITT population was to be the primary population for the efficacy analysis. Membership in the analyses populations was to be determined before unblinding. The primary efficacy analysis did not impute missing data; it used all observed data (except when rescue medication was received 12 hours before an efficacy assessment) in a restricted maximum likelihood (REML)-based mixed model for

repeated measures (MMRM) analysis. The model used all available data from all subjects to derive an estimate of pain intensity scores for subjects following trial withdrawal, rather than "imputing" a score for individual subjects. This MMRM model has limitations given it assumes data is missing at random. If subjects were to receive rescue medication within 12 hours before the efficacy assessments at a trial visit, their efficacy assessments at that visit were to be disregarded and considered missing. This was determined prior to any efficacy analysis.

A sensitivity analysis was performed on the primary efficacy variable (change from Baseline in WOMAC Pain Subscale score to Week 12) by using modified Baseline observation carried forward (mBOCF) imputed data. Imputation due to rescue medication was performed prior to all other imputation. Values were to be imputed in the following manner:

- BOCF for subjects who withdrew from the trial because of an AE/intolerance to trial drug
- Reasons other than an AE/intolerance to trial drug, missing values were imputed by using the LOCF
- Intermittent missing assessments for a scheduled visit before subject completion or discontinuation were imputed to be imputed using LOCF
- For subjects who took rescue medication within 12 hours (inclusively) prior to the efficacy assessments at a visit, the assessments at that visit were to be disregarded. Instead, the assessments at that visit were to be imputed by using the LOCF

Unless otherwise indicated, all statistical tests were to be 2-sided. A significance level of 0.05 was to be used for the primary efficacy analysis. Sequential testing was to be applied for the primary efficacy analysis comparing each of the diclofenac doses with placebo. All analyses were performed using SAS® Software Version 9.1.3.

Results

Subject Overview

A total of 305 subjects were randomized into the trial and all were included in the ITT and safety population. All randomized and treated subjects were evaluated for TEAEs. The subjects were randomized into three groups:

- Diclofenac 35 mg BID (n=104)
- Diclofenac 35 mg TID (n=98)
- Placebo (n=103)

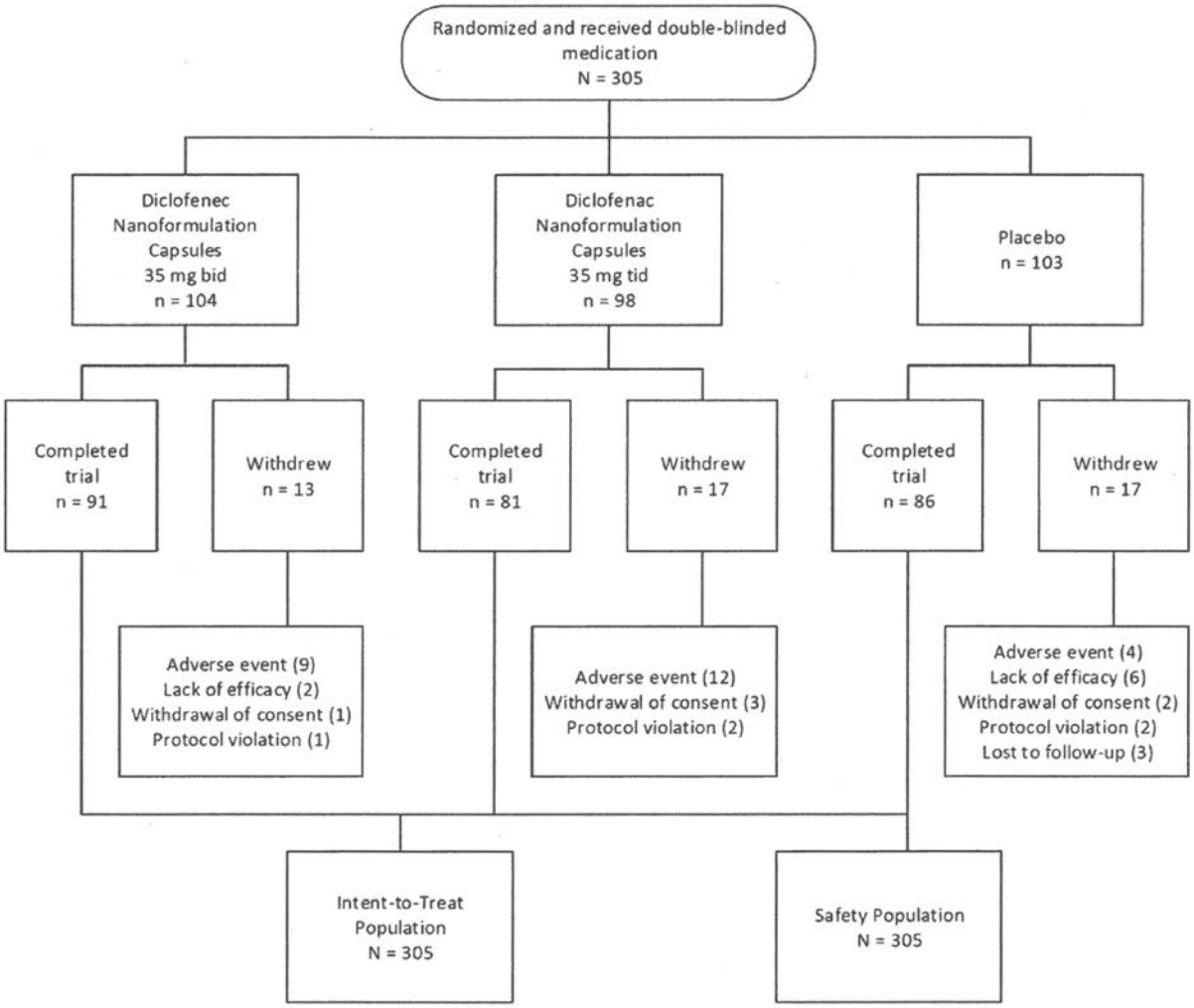
Subject Disposition

The majority of subjects (258 subjects [84.6%]) completed the trial. A total of 25 subjects (8.2%) across the 3 treatment groups withdrew from the trial secondary to an AE: 12 subjects (12.2%) from the diclofenac TID group, 9 subjects (8.7%) from the diclofenac BID group, and 4 subjects (3.9%) from the placebo group. A total of 8 subjects (2.6%) withdrew for lack of efficacy: 2 subjects (1.9%) from diclofenac BID group and 6 subjects (5.8%) from the placebo group. Refer to the figure below (Figure 2) for subject disposition in the controlled trial.

Case report forms and narratives were requested by the Division for all subjects who withdrew due to "withdrew consent" to determine whether this represented additional safety dropouts. I reviewed

through the CRFs/narratives and no apparent safety concerns related to the drug were revealed. Two subjects (114-013 and 119-005) developed AEs during the trial and were within the diclofenac TID group. The AEs do not appear related to the study drug (sinusitis and fall causing traumatic pain) and should not have an effect on the safety analysis.

Figure 2: Subject Disposition Flowchart



Source: Applicant's clinical study report DIC3-08-05, p. 56

Demographics

The demographics were generally comparable across treatment groups in the study (Table 6). The Safety population was diverse, consisting of American Indian, Asian, Black or African American,

native Hawaiian, and White males and females. However, the trial population was predominantly female 203 subjects (66.6%) and white 245 subjects (80.3%). The mean age (SD) was 61.6 (8.87).

Table 6: DIC3-08-05 Demographics Characteristics

Variable	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98	Total N=305
Age (years)				
N	103	104	98	305
Mean (SD)	61.8 (8.42)	61.4 (8.33)	61.7 (9.90)	61.6 (8.87)
Median	61.0	60.0	61.0	61.0
Minimum, maximum	(45, 82)	(46, 86)	(41, 90)	(41, 90)
Gender, n (%)				
Male	32 (31.1%)	40 (38.5%)	30 (30.6%)	102 (33.4%)
Female	71 (68.9%)	64 (61.5%)	68 (69.4%)	203 (66.6%)
Race, n (%)				
American Indian or Alaska Native	0	1 (1.0%)	0	1 (0.3%)
Black or African American	20 (19.4%)	23 (22.1%)	14 (14.3%)	57 (18.7%)
Native Hawaiian or Other Pacific Islander	0	1 (1.0%)	0	1 (0.3%)
White or Caucasian	82 (79.6%)	80 (76.9%)	83 (84.7%)	245 (80.3%)
Other	1 (1.0%)	0	1 (1.0%)	2 (0.7%)
Ethnicity, n (%)				
Hispanic or Latino	8 (7.8%)	7 (6.7%)	2 (2.0%)	17 (5.6%)
Not Hispanic or Latino	95 (92.2%)	97 (93.3%)	96 (98.0%)	288 (94.4%)
Weight (kg)				
Mean (SD)	89.44 (17.991)	88.16 (17.037)	89.35 (16.552)	88.97 (17.167)
Median	89.60	86.65	88.65	88.60
Minimum, maximum	(49.0, 133.3)	(52.8, 152.5)	(58.5, 124.8)	(49.0, 152.5)
Height (cm)				
Mean (SD)	168.70 (9.245)	169.91 (10.561)	167.60 (9.794)	168.76 (9.898)
Median	167.60	170.10	165.10	167.60
Minimum, maximum	(152.8, 193.0)	(148.6, 198.1)	(149.9, 192.0)	(148.6, 198.1)
Body mass index, kg/m^2				
Mean (SD)	31.3 (5.18)	30.6 (5.18)	31.8 (5.09)	31.2 (5.16)
Median	31.0	30.0	31.0	31.0
Minimum, maximum	(17, 40)	(21, 40)	(21, 42)	(17, 42)

Source: Section 14.1, Table 14.1.2

Source: Applicant's clinical study report DIC3-08-05, p.59

The predominance of female subjects is reflective of and consistent with the epidemiology of the underlying disease process, osteoarthritis. The demographic characteristics were generally balanced across the 4 treatment groups.

Screening/Baseline Disease Characteristics

To qualify for trial entry, patients were required to have experienced an acceptable flare of OA pain following discontinuation of NSAID or acetaminophen treatment at the screening visit. Although the Division no longer recommends flare designs, DIC3-08-05 was already underway and deemed appropriate prior to this determination. Therefore, the Division agreed the study design with the flare component was acceptable for this application. Specifically, the entry requirements were to be a minimum mean WOMAC Pain Subscale score of 40 mm (on a 100 mm scale), coupled with an increase in the WOMAC Pain Subscale score of ≥15 mm. Baseline WOMAC Pain Subscale scores were similar across treatment groups (Table 4). The mean (SD) WOMAC Pain Subscale score at baseline was 74.93 (15.61) mm, nearly double the minimum score required for trial entry. This indicates the study population represents patients who suffer from a significant pain burden.

Table 7: Summary of Baseline Characteristics – DIC3-08-05

Variable Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98	Total N=305
Baseline WOMAC Pain Subscale score				
N	103	104	98	305
Mean (SD)	75.27 (17.27)	73.42 (15.22)	76.18 (14.15)	74.93 (15.61)
Median	79.00	74.70	77.50	76.80
Minimum[a], maximum	(14.2, 98.2)	(11.2, 99.6)	(40.2, 100.0)	(11.2, 100.0)
Baseline Total (Composite) WOMAC score				
N	100	100	94	294
Mean (SD)	71.60 (17.24)	70.26 (15.69)	72.83 (15.87)	71.54 (16.27)
Median	74.00	70.80	75.45	73.60
Minimum, maximum	(16.2, 98.1)	(39.4, 99.1)	(33.4, 100.0)	(16.2, 100.0)
Missing	3	4	4	11
Baseline Pain Intensity VAS score				
N	100	100	94	294
Mean (SD)	71.5 (18.82)	69.6 (19.99)	71.8 (19.33)	71.0 (19.35)
Median	74.5	73.5	74.5	74.0
Minimum, maximum	(18, 97)	(4, 100)	(5, 100)	(4, 100)
Missing	3	4	4	11

Source: Section 14.1, Table 14.1.2

Source: Applicant's clinical study report DIC3-08-05, p.61

Prior and Concomitant Drug Treatments

Prior medications were defined as medications received prior to the first administration of the trial drug. Almost all the subjects used some prior medications but a review of the tables provided by the

Applicant did not shown a significant difference across treatment groups. Concomitant medications were defined as any medications other than the trial drug that a subject received concurrently with the trial drug. Concomitant medications were generally balanced across treatment groups (Table 8). The most frequent concomitant medications overall included acetylsalicylic acid (73 subjects [23.9%]) and multivitamins (63 subjects [21.6%]). Acetylsalicylic acid was allowed as a concomitant medication for cardiovascular prophylaxis and not as a treatment for osteoarthritis pain.

Table 8: Summary of Concomitant Medications Received by at Least 10% of Subjects Across Treatment Groups by ATC Class and Preferred Term

ATC Class Preferred Term	Placebo n=103 n (%)	Diclofenac Nanoformulation Capsules 35 mg bid n=104 n (%)	35 mg tid n=98 n (%)	All n=202 n (%)	Total n=305 n (%)
Subjects with ≥1 concomitant medication[a]	91 (88.3)	89 (85.6)	96 (98.0)	185 (91.6)	276 (90.5)
HMG COA reductase inhibitors	**31 (30.1)**	**30 (28.8)**	**32 (32.7)**	**62 (30.7)**	**93 (30.5)**
Simvastatin	15 (14.6)	16 (15.4)	18 (18.4)	34 (16.8)	49 (16.1)
Salicylic acid and derivatives	**23 (22.3)**	**19 (18.3)**	**25 (25.5)**	**44 (21.8)**	**67 (22.0)**
Acetylsalicylic acid	25 (24.3)	21 (20.2)	27 (27.6)	48 (23.8)	73 (23.9)
Multivitamins, plain	**25 (24.3)**	**25 (24.0)**	**17 (17.3)**	**42 (20.8)**	**67 (22.0)**
Multivitamins, plain	25 (24.3)	24 (23.1)	17 (17.3)	41 (20.3)	66 (21.6)
ACE inhibitors, plain	**23 (22.3)**	**14 (13.5)**	**14 (14.3)**	**28 (13.9)**	**51 (16.7)**
Lisinopril	15 (14.6)	12 (11.5)	9 (9.2)	21 (10.4)	36 (11.8)
Other lipid modifying agents	**20 (19.4)**	**18 (17.3)**	**13 (13.3)**	**31 (15.3)**	**51 (16.7)**
Fish oil	17 (16.5)	16 (15.4)	12 (12.2)	28 (13.9)	45 (14.8)
Vitamin D analogues	**18 (17.5)**	**18 (17.3)**	**15 (15.3)**	**33 (16.3)**	**51 (16.7)**
Vitamin D	11 (10.7)	11 (10.6)	10 (10.2)	21 (10.4)	32 (10.5)
Thyroid hormones	**12 (11.7)**	**18 (17.3)**	**18 (18.4)**	**36 (17.8)**	**48 (15.7)**
Levothyroxine sodium	6 (5.8)	11 (10.6)	14 (14.3)	25 (12.4)	31 (10.2)
Proton pump inhibitors	**13 (12.6)**	**15 (14.4)**	**16 (16.3)**	**31 (15.3)**	**44 (14.4)**
Thiazides, plain	**11 (10.7)**	**17 (16.3)**	**14 (14.3)**	**31 (15.3)**	**42 (13.8)**
Hydrochlorothiazide	11 (10.7)	17 (16.3)	14 (14.3)	31 (15.3)	42 (13.8)
Biguanides	**14 (13.6)**	**7 (6.7)**	**13 (13.3)**	**20 (9.9)**	**34 (11.1)**
Metformin	13 (12.6)	6 (5.8)	13 (13.3)	19 (9.4)	32 (10.5)
Beta blocking agents, selective	**9 (8.7)**	**11 (10.6)**	**11 (11.2)**	**22 (10.9)**	**31 (10.2)**

Source: Section 14.3.4, Post-hoc Table 14.3.4.1. and Post-hoc Table 14.3.4.2

Source: Applicant's clinical study report DIC3-08-05, p. 147

Protocol Violations/Deviations

There were a total of 114 subjects (37.4%) for whom protocol deviations were reported related to trial drug compliance. These occurred in generally similar numbers across the 3 treatment groups. There were 24 subjects with protocol deviations that were deemed to be major deviations. Five subjects had "other" major protocol deviations, including use of prohibited medications, rescue medication compliance violations, missing assessments, and incorrectly timed trial drug administration.

Dosing Information
The planned duration of double-blind treatment was to be throughout a 12-week treatment period.

Efficacy Results

Overview
The Applicant's analysis demonstrated the superiority of diclofenac 35 mg TID dosing with respect to placebo for the primary endpoint being the mean change from Baseline in WOMAC Pain Subscale scores (difference between Baseline score and the Week 12 [V5] assessment). Results for the ITT population are presented for the primary and secondary efficacy variables. A number of sensitivity analyses were also performed to test the robustness of the findings. The description of the following results represents the Applicant's findings. My interpretation of the results is covered in Section 6. No secondary endpoints were identified as key endpoints.

Primary endpoint results:
- A statistically significant treatment benefit was observed for the diclofenac 35 mg TID group compared to placebo (P=0.0024) as measured by the primary efficacy parameter, the least squares (LS) mean change in WOMAC Pain Subscale score from Baseline to Week 12/ET
- A lack of statistical significance was achieved for the primary efficacy comparison of the diclofenac 35 mg BID group vs. placebo (P=0.0795) based on the change from Baseline in WOMAC Pain Subscale score at Week 12/ET

Secondary endpoints (none identified as key):
- Mean change from Baseline in the WOMAC Pain Subscale score at Week 2 and Week 6
- Mean change from Baseline in the WOMAC Pain Subscale score and the average WOMAC Pain Subscale over 12 weeks
- Mean change from Baseline in the average Total (Composite) WOMAC score over 12 weeks
- Mean change from Baseline in the VAS Pain Intensity and the average VAS Pain Intensity over 12 weeks
- Patient Global Impression of Change and Clinical Global Impression of Change scores at Week 12
- Amount of rescue medication received by each subject
- Cumulative discontinuations due to lack of efficacy at Week 12
- Mean changes from Baseline at Week 12/ET in SF-36v2™ Mental Component Summary (MCS) and Physical Component Summary (PCS) scores
- Responder rates for subjects with ≥30% and for subjects with ≥50% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively), as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS Pain Intensity scores

- Continuous responder rates for subjects who achieved a reduction in pain, evaluated at a continuous cutoff ranging from 0% to 100% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively) as assessed on the basis of WOMAC Pain Subscale scores and separately on the basis of VAS Pain Intensity scores
- Subgroup analyses of mean change from Baseline in WOMAC Pain Subscale scores at Week 12/ET

Post-hoc efficacy analyses

- Additional sensitivity analyses to test the assumptions of the MMRM model
- Mean change from Baseline in WOMAC Function Subscale scores, WOMAC Stiffness Subscale scores, and Total (Composite) WOMAC scores at each scheduled visit (and over the 12-week period if not previously determined)
- Mean change from Baseline in each SF-36v2™ subdomain at Week 12/ET
- Responder rates for subjects with ≥10 mm reduction in WOMAC Pain Subscale score and Pain Intensity score measured by VAS from Baseline at Weeks 2, 6, and 12/ET
- Silverman Integrated Rank Analysis to explore the effect of rescue medication usage on the results of the primary efficacy endpoint
- Analyses of the CGIC and PGIC to determine the odds ratio for reporting "very much improved" or "much improved" vs "very much worse" or "much worse"

Primary Efficacy Results

The primary efficacy endpoint was the change from Baseline to Week 12/ET in the WOMAC Pain Subscale score. For the WOMAC Pain Subscale, subjects were asked to recall the pain felt in the target joint (knee or hip) while performing various tasks or at rest during the previous 24-hour period. The original protocol-defined primary efficacy analysis was performed using a REML-based MMRM analysis. The model used all available data from all subjects to derive an estimate of pain intensity scores for subjects following trial withdrawal, rather than imputing a score for individual subjects. If a subject received rescue medication within 12 hours before the efficacy assessments at a visit, the efficacy assessments at that visit were disregarded and considered missing.

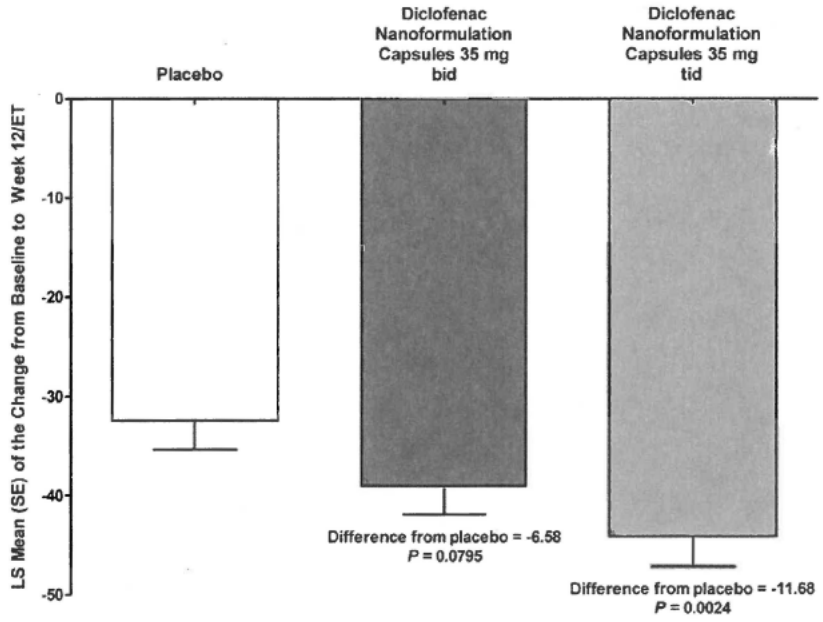
Table 9 below shows the primary analysis. The LS mean (SE) changes from Baseline to Week 12/ET in WOMAC Pain Subscale scores were numerically greater for subjects in both active treatment groups compared with placebo: -44.14 (3.070) mm for the diclofenac 35 mg TID treatment group, -39.04 (2.905) mm for the diclofenac 35 mg BID treatment group, and -32.46 (2.937) mm for the placebo treatment group. However, only the TID group showed statistical significance compared to the placebo group for the primary endpoint (P=0.0024). The diclofenac BID group did show a trend towards improvement in pain, but did not reach statistical significance (Figure 3).

Table 9: Primary Efficacy Analysis (MMRM Analysis) of WOMAC Pain Subscale Scores at Week 12/ET – ITT Population

Visit Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98
Baseline, n	103	104	98
N			
Mean (SD)	75.27 (17.27)	73.42 (15.22)	76.18 (14.16)
Week 12/ET, n	96	102	96
Mean (SD)	42.98 (27.37)	35.65 (27.60)	31.47 (24.23)
Change from Baseline to Week 12/ET, n	96	102	96
LS mean (SE)[a]	-32.46 (2.937)	-39.04 (2.905)	-44.14 (3.070)
95% CI[a]	(-38.24, -26.68)	(-44.76, -33.32)	(-50.18, -38.10)
Comparison vs placebo[a]			
Difference in LS mean (SE)	--	-6.58 (3.739)	-11.68 (3.806)
95% CI for difference	--	(-13.94, 0.78)	(-19.17, -4.19)
P value for difference	--	0.0795	0.0024

Source: Applicant's Clinical Study Report, Table 11-3, p. 63

Figure 3: Mean Change From Baseline in WOMAC Pain Subscale Scores to Week 12/ET – Mixed Model for Repeated Measures Analysis – ITT Population



Source: Applicant's Clinical Study Report, Figure 11-1, p. 64

The Applicant also performed sensitivity analyses of the primary efficacy endpoint (Table 10). Please see Mr. David Petullo's report for a detailed description of the statistical analyses. The sensitivity analyses were performed due to the potential for bias regarding missing data in the Mixed Model for Repeated Measures (MMRM) model. The MMRM assumes that missing data is missing at random. This assumption may cause patients who discontinued treatment due to an adverse event appear to have had treatment benefit. Therefore, the sensitivity analyses were performed to examine the missing at random assumption. The sensitivity analyses produced similar results to those obtained with the primary MMRM analysis and therefore supports the finding of efficacy for the treatment of osteoarthritis pain for the diclofenac TID group.

Table 10: Sensitivity Analyses of WOMAC Pain Subscale Scores at Week 12/ET – ITT Population

Analysis Model Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98
Penalized MMRM[a]			
LS Mean (SE)[b]	-30.74 (2.944)	-38.00 (2.914)	-41.93 (3.078)
95% CI[b]	(-36.54, -24.95)	(-43.74, -32.27)	(-47.98, -35.87)
Comparison vs placebo[b]			
Difference in LS mean (SE)	--	-7.26 (3.751)	-11.19 (3.818)
95% CI for difference	--	(-14.65, 0.12)	(-18.70, -3.67)
P value for difference	--	0.0539	0.0037
Post-hoc penalized MMRM (modified model)[c]			
LS Mean (SE)[b]	-30.82 (2.951)	-37.69 (2.921)	-42.00 (3.085)
95% CI[b]	(-36.63, -25.01)	(-43.44, -31.94)	(-48.07, -35.93)
Comparison vs placebo[b]			
Difference in LS mean (SE)	--	-6.87 (3.760)	-11.18 (3.827)
95% CI for difference	--	(-14.27, 0.54)	(-18.71, -3.64)
P value for difference	--	0.0689	0.0038
ANCOVA (mBOCF data imputation)			
LS Mean (SE)[d]	-31.37 (3.114)	-37.85 (3.127)	-40.87 (3.320)
95% CI[d]	(-37.51, -25.24)	(-44.01, -31.70)	(-47.40, -34.33)

Comparison vs placebo[d]			
Difference in LS mean (SE)	--	-6.48 (3.901)	-9.49 (3.977)
95% CI for difference	--	(-14.16, 1.20)	(-17.32, -1.66)
P value for difference	--	0.0979	0.0177
Pattern-mixture model			
LS Mean (SE)[e]	-31.98 (2.923)	-38.92 (2.939)	-43.90 (3.116)
95% CI[e]	(-37.70, -26.25)	(-44.68, -33.16)	(-50.00, -37.79)
Comparison vs placebo[e]			
Difference in LS mean (SE)	--	-6.95 (3.746)	-11.92 (3.825)
95% CI for difference	--	(-14.29, 0.39)	(-19.42, -4.42)
P value for difference	--	0.0636	0.0018

Source: Applicants clinical study report, Table11-4, p. 66

Secondary Efficacy Results

The following are a summary of the Applicant's results. None of the secondary endpoints were identified as key and the Applicant did not control for multiplicity. In general, I believe the secondary endpoints are supportive of efficacy for the indication of treatment of osteoarthritis pain for the TID dose, but not for the BID dose.

- WOMAC Pain Subscale Scores at Weeks 2 and 6
  - Both treatment groups achieved reductions in WOMAC Pain Subscale, similar to the results observed at Week 12, however the reduction was more evident in subjects in the TID treatment group compared with subjects in the BID treatment group (Table 11)

Table 11: WOMAC Pain Subscale Scores at Weeks 2 and 6 and the Change From Baseline – ITT Population

Visit Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98
Baseline, n	103	104	98
Mean (SD)	75.27 (17.27)	73.42 (15.22)	76.18 (14.16)
Week 2, n	92	100	94
Mean (SD)	52.80 (25.86)	43.10 (25.89)	38.79 (26.62)
Week 6, n	87	91	86
Mean (SD)	44.05 (26.04)	36.08 (26.71)	31.70 (23.75)
Change from Baseline to Week 2, n	92	100	94
LS Mean (SE)[a]	-21.60 (2.787)	-31.40 (2.742)	-37.42 (2.907)
95% CI	(-27.08, -16.11)	(-36.80, -26.00)	(-43.14, -31.69)
Comparison vs placebo[a]			
Difference in LS Mean (SE)	--	-9.80 (3.481)	-15.82 (3.552)
95% CI for difference	--	(-16.66, -2.95)	(-22.82, -8.83)
P value for difference	--	0.0052	<0.0001
Change from Baseline to Week 6, n	87	91	86
LS Mean (SE)[a]	-31.08 (2.922)	-36.64 (2.889)	-43.51 (3.051)
95% CI	(-36.83, -25.33)	(-42.32, -30.95)	(-49.51, -37.50)
Comparison vs placebo[a]			
Difference in LS mean (SE)	--	-5.56 (3.707)	-12.43 (3.776)
95% CI for difference	--	(-12.86, 1.74)	(-19.87, -4.99)
P value for difference	--	0.1349	0.0011

Source: Applicant's clinical study report, Table11-5, p. 70

- Average 12-week change WOMAC Pain Subscale Score From Baseline
  - Greater LS mean changes from Baseline for the 12-week average were observed for both diclofenac treatment groups (-13.24 mm for the TID group [P=0.0001] and -7.48 mm for the BID group [P=0.0248]) compared with placebo
- Total (Composite) WOMAC
  - Treatment effects were also assessed using the Total (Composite) WOMAC score, which includes information on function and stiffness, in addition to pain
  - The TID (P≤0.0036) and BID (P≤0.0909) treatment group achieved greater reductions in the Total (Composite) WOMAC score from baseline over 2, 6, and 12 weeks as well as the average score over the 12-week period also greater for the diclofenac TID (P=0.0002) and BID (P=0.0363) groups compared with placebo (Table 12)

Table 12: Total (Composite) WOMAC Scores at Each Trial Visit and Over the 12-Week Period – ITT Population

Visit Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	Diclofenac Nanoformulation Capsules 35 mg tid n=98
Baseline, n	100	100	94
Mean (SD)	71.60 (17.241)	70.26 (15.692)	72.83 (15.866)
Week 2, n	92	100	94
Mean (SD)	52.87 (25.397)	45.13 (25.969)	40.54 (26.559)
Week 6, n	87	91	86
Mean (SD)	46.14 (25.461)	37.28 (26.744)	33.81 (24.434)
Week 12/ET, n	96	102	96
Mean (SD)	45.55 (27.155)	38.28 (28.575)	34.35 (24.451)
12-week average[a], n	100	104	98
Mean (SD)	48.35 (24.27)	40.86 (25.14)	37.30 (23.62)

Source: Applicant's clinical study report, Table11-7, p. 73

- WOMAC Function and Stiffness Subscale Scores (post-hoc analyses)
  - The treatment groups achieved lower mean scores at each post-baseline trial visit and over the 12-week trial period compared with the placebo group (Table 13)
  - Mean scores for the TID treatment group were lower overall and at 12 weeks the TID group showed statistical significance (p=0.0053)

Table 13: WOMAC Function Subscale Scores at Weeks 2, 6, and 12/ET – ITT Population

Visit Statistics	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Baseline, n	99	100	94
Mean (SD)	69.85 (18.736)	68.65 (17.845)	71.46 (18.103)
Week 2, n	92	100	94
Mean (SD)	52.53 (25.585)	45.52 (26.481)	40.91 (26.880)
Week 6, n	87	91	85
Mean (SD)	46.26 (25.875)	37.44 (27.010)	34.07 (24.808)
Week 12/ET, n	96	102	95
Mean (SD)	45.90 (27.606)	38.92 (29.990)	34.59 (24.711)
12-week average[a], n	100	104	98
Mean (SD)	48.39 (24.584)	41.23 (25.574)	37.87 (23.941)

Source: Applicant's clinical study report, Table11-9, p. 76

- Changes in pain intensity with the Visual Analog Scale (VAS)
  - Subjects used a standard 100 mm VAS to quantify pain intensity at the time of each scheduled trial visit and used to evaluate changes in pain intensity Baseline to the average over the 12-week trial period
  - Greater reductions achieved by subjects in the TID treatment group compared with placebo and the diclofenac BID group
  - The trial was not powered to assess the treatment effect of diclofenac 35 mg based on VAS, however numerically greater reductions in pain intensity for both treatment groups were observed compared to placebo
- Responder analysis
  - Responder rates for subjects experiencing ≥30% reduction in pain intensity from baseline on WOMAC pain subscale
    - The TID group showed statistical significance by week 2 and continued through week 12 (Table 14)

Table 14: Responder Rates for Subjects with at Least 30% Reduction in the WOMAC Pain Subscale Score From Baseline

Subjects with ≥30% Reduction from Baseline to Each Visit	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Week 2, n	92	100	94
Subjects with reduction, n (%)	42 (45.7)	60 (60.0)	63 (67.0)
P value[a]	--	0.0466	0.0033
Week 6, n	87	91	86
Subjects with reduction, n (%)	47 (54.0)	63 (69.2)	65 (75.6)
P value[a]	--	0.0369	0.0030
Week 12/ET, n	96	102	96
Subjects with reduction, n (%)	58 (60.4)	70 (68.6)	75 (78.1)
P value[a]	--	0.2271	0.0078

Source: Applicant's clinical study report, Table11-12, p. 82

- Responder rates for subjects with at least 50% reduction in the WOMAC Pain Subscale Score from baseline
  - Similar to the ≥30% reduction analysis, only the TID group showed statistical significance through the trial (Table 15)

Table 15: Responder Rates for Subjects with at Least 50% Reduction in the WOMAC Pain Subscale Score

Subjects with ≥50% Reduction from Baseline to Each Visit	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Week 2, n	92	100	94
Subjects with reduction, n (%)	26 (28.3%)	43 (43.0%)	50 (53.2%)
P value[a]	--	0.0335	0.0005
Week 6, n	87	91	86
Subjects with reduction, n (%)	36 (41.4%)	52 (57.1%)	52 (60.5%)
P value[a]	--	0.0355	0.0120
Week 12/ET, n	96	102	96
Subjects with reduction, n (%)	44 (45.8%)	57 (55.9%)	60 (62.5%)
P value[a]	--	0.1575	0.0205

Source: Applicant's clinical study report, Table11-13, p. 83

- Responder rates for subjects with at least 30% reduction in pain intensity measured by the VAS
  - Clear differences were only evident for the TID treatment group with significant difference apparent by week 2 (Table 16)

Table 16: Responder Rates for Subjects with at Least 30% Reduction in VAS Pain Intensity Score From Baseline to Each Scheduled Visit – ITT Population

Subjects with ≥30% Reduction from Baseline to Each Visit	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Week 2, n	90	96	91
Subjects with reduction, n (%)	48 (53.3%)	59 (61.5%)	63 (69.2%)
P value[a]	--	0.2626	0.0281
Week 6, n	84	88	82
Subjects with reduction, n (%)	55 (65.5%)	59 (67.0%)	65 (79.3%)
P value[a]	--	0.8277	0.0471
Week 12/ET, n	93	98	93
Subjects with reduction, n (%)	59 (63.4%)	70 (71.4%)	70 (75.3%)
P value[a]	--	0.2386	0.0802

Source: Applicant's clinical study report, Table 11-5, p.85

- Responder rates for subjects with at least 30% reduction in pain intensity measured by the VAS
  - Only the TID treatment group showed any statistical significance in this category and the differences from placebo were significant only at Week 2 (Table 17)

Table 17: Responder Rates for Subjects with at Least 50% Reduction in the VAS Pain Intensity Score From Baseline to Each Scheduled Visit – ITT Population

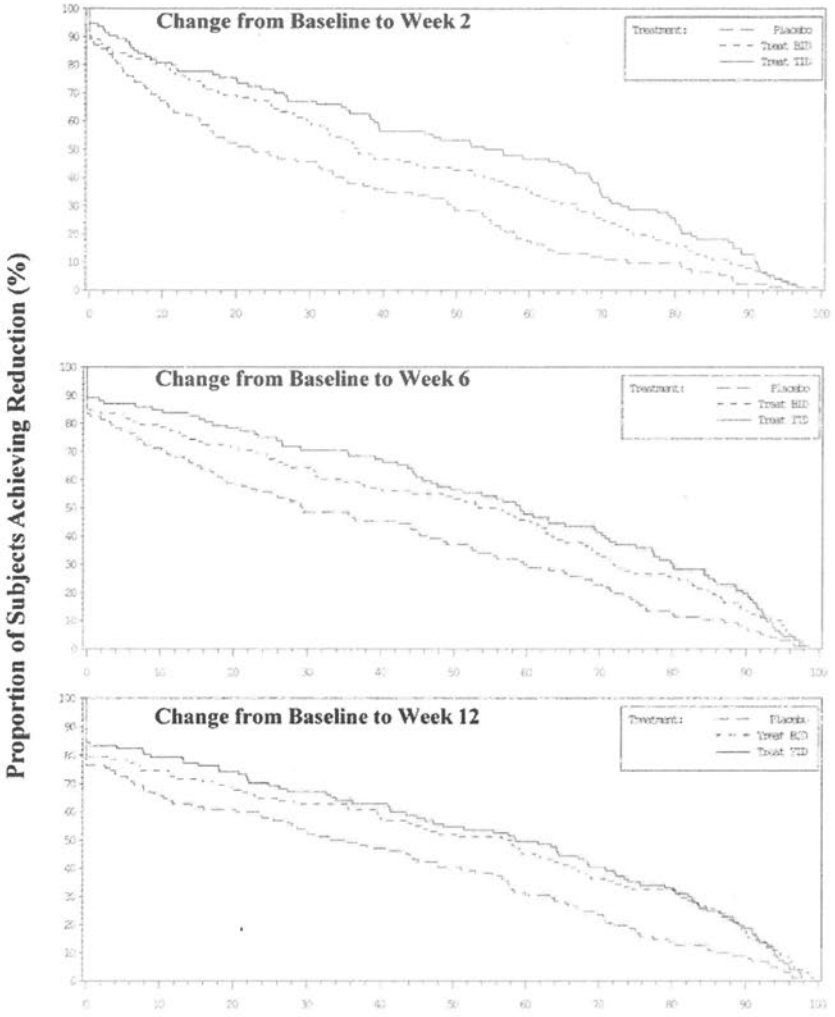
Subjects with ≥ 50% Reduction from Baseline to Each Scheduled Visit	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Week 2, n	90	96	91
Subjects with reduction, n (%)	35 (38.9%)	47 (49.0%)	51 (56.0%)
P value[a]	--	0.1669	0.0208
Week 6, n	84	88	82
Subjects with reduction, n (%)	50 (59.5%)	50 (56.8%)	53 (64.6%)
P value[a]	--	0.7192	0.4975
Week 12/ET, n	93	98	93
Subjects with reduction, n (%)	45 (48.4%)	59 (60.2%)	55 (59.1%)
P value[a]	--	0.1012	0.1414

Source: Applicant's clinical study report, Table 11-6, p.86

- Post-hoc analysis for responder rates experiencing at least 10 mm reduction in the VAS
  - At each scheduled visit, a numerically higher proportion of subjects in the diclofenac 35 mg TID and BID treatment groups achieved ≥10 mm reduction in pain intensity compared with placebo; however, the difference was significant only at Week 6 for the TID treatment group (P=0.0046)
- Continuous Responder Analysis[10]
  - Continuous responder analyses were conducted at Week 2, Week 6, and Week 12 based on the WOMAC Pain Subscale scores and the VAS Pain Intensity scores
  - WOMAC Pain Subscale
    - The separation in the curves for the active treatment arms vs the placebo curve was less distinct for the 35 mg BID group than the TID group at Week 2 and Week 6 but similar by week 12 (Figure 4)
    - This finding suggests a quicker response with the TID dosing
  - VAS Pain Intensity Scores
    - There is a clear separation of the curves compared with placebo for the BID and TID treatment groups, once again favoring the tid group in time to onset of a response (Figure 5)

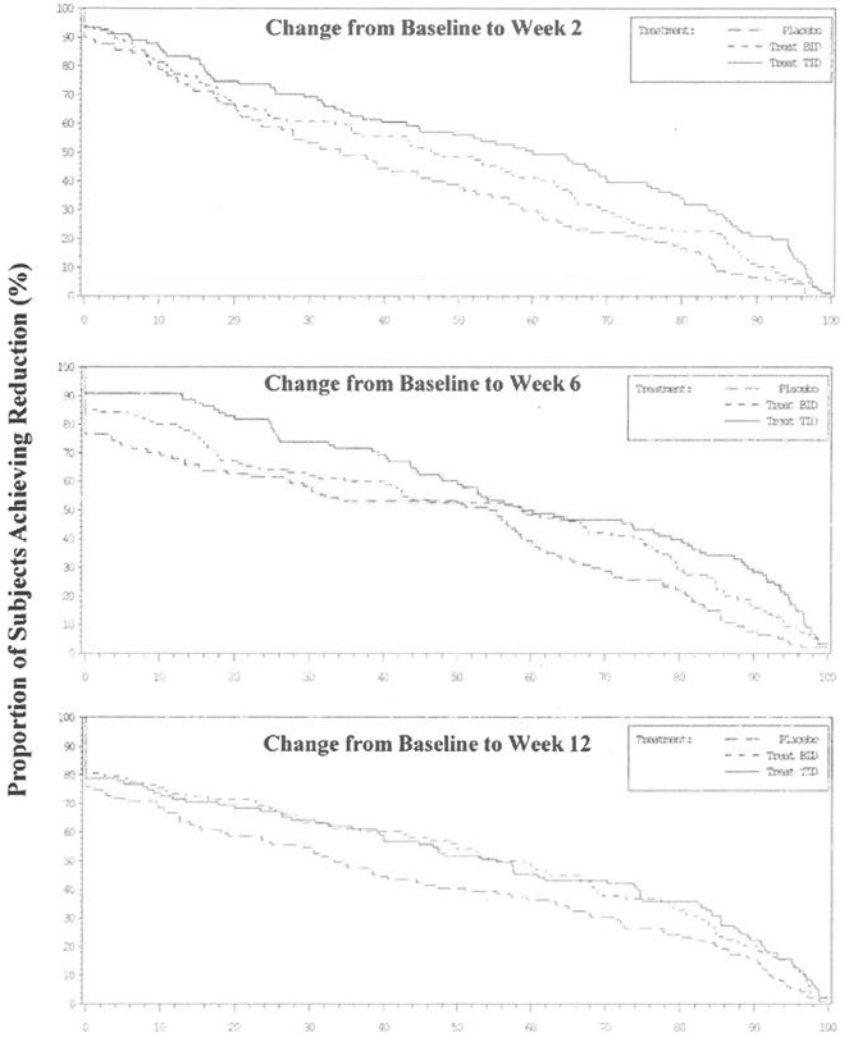
[10] Responder was defined as any subject achieving a reduction in pain ranging from 0% to 100%. Nonresponders were subjects who experienced increases in pain, or withdrew early from the trial.

Figure 4: Continuous Responder Analysis of the Proportion of Patients Achieving Reductions in WOMAC Pain Subscale Scores – ITT Population



Source: Applicant's clinical study report, Figure 11-6, p.89

Figure 5: Continuous Responder Analysis of the Proportion of Subjects Achieving Reductions in VAS Pain Intensity Scores – ITT Population



Source: Applicant's clinical study report, Figure 11-7, p.90

- Patient and Clinical Global Impression of Change
  - Both treatment groups reported favorable global impressions of the change (PGIC and CGIC) in their status from baseline to Week 12 compared with placebo (Table 18)
  - The statistically significant difference from placebo for both groups, especially assessments of "very much improved" and "much improved", suggest clinically relevant benefits of the active treatments

Table 18: Patient Global Impression of Change and Clinical Global Impression of Change Scores at Week 12 – ITT Population

Global Impression of Change	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Patient Global Impression of Change, n (%)			
Very much improved	6 (6.3)	23 (22.5)	25 (26.0)
Much improved	27 (28.1)	29 (28.4)	39 (40.6)
Minimally improved	28 (29.2)	31 (30.4)	20 (20.8)
No change	22 (22.9)	11 (10.8)	9 (9.4)
Minimally worse	4 (4.2)	6 (5.9)	2 (2.1)
Much worse	7 (7.3)	1 (1.0)	1 (1.0)
Very much worse	2 (2.1)	1 (1.0)	0
P value[a]	--	<0.001	0.0008
Odds ratio for being "very much improved" or "much improved" vs "much worse" or "very much worse" (95% CI)	--	7.09 (1.44, 34.88)	17.45 (2.12, 143.72)
P value[a]	--	0.0071	0.0006
Clinical Global Impression of Change, n (%)			
Very much improved	6 (6.3)	21 (20.6)	18 (18.8)
Much improved	28 (29.2)	32 (31.4)	47 (49.0)
Minimally improved	22 (22.9)	27 (26.5)	18 (18.8)
No change	26 (27.1)	15 (14.7)	11 (11.5)
Minimally worse	5 (5.2)	5 (4.9)	2 (2.1)
Much worse	6 (6.3)	1 (1.0)	0
Very much worse	3 (3.1)	1 (1.0)	0
P value[a]	--	<0.001	0.0005
Odds ratio for being "very much improved" or "much improved" vs "much worse" or "very much worse" (95% CI)	--	7.01 (1.43, 34.45)	36.07 (2.04, 638.47)
P value[a]	--	0.0074	0.0001

Source: Applicant's clinical study report, Table11-18, p.92

- Rescue Medication[11]
  - The majority of subjects (approximately 90%) in all treatment groups received ≥1 dose of rescue medication at any time during the trial
  - The amount of rescue medication usage may be an indicator of efficacy, however, there was no statistical significance between groups for overall rescue usage (Table 19)

[11] Patients enrolled in the trial could receive acetaminophen as needed up to 3000 mg per day as rescue medication

Table 19: Summary of Rescue Medication Use – ITT Population

Subjects Taking Rescue Medication	Placebo n=103	Diclofenac Nanoformulation Capsules	
		35 mg bid n=104	35 mg tid n=98
Number and percentage of subjects taking rescue medication, n (%)	92 (89.3)	95 (91.3)	89 (90.8)
P value[a]	--	0.6218	0.7232
Number of doses of rescue medication taken by each subject, n	91	95	89
LS Mean (SE)[b]	92.2 (9.93)	75.4 (9.39)	74.2 (10.43)
95% CI[a]	(72.7, 111.8)	(56.9, 93.9)	(53.6, 94.7)
Comparison vs placebo[b]			
Difference in LS mean (SE)	--	-16.8 (12.04)	-18.1 (12.12)
95% CI for difference	--	(-40.5, 6.9)	(-41.9, 5.8)
P value for difference	--	0.1635	0.1372

Source: Applicant's clinical study report, Table11-20, p.98

Safety Findings

A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7.

Deaths

No deaths occurred during the trial.

Serious Adverse Events (SAEs)

There were no serious CV, GI or renal TEAEs of the type that have been associated with NSAID usage reported during the trial.

Discontinuations Due to Adverse Events

Twenty-five subjects (8.2%) withdrew from the trial due to a TEAE. Twenty-one subjects (10.4%) in the 2 diclofenac groups and 4 subjects (3.9%) in the placebo group experienced events leading to discontinuation. Ten subjects in the combined diclofenac groups withdrew due to gastrointestinal disorders including diarrhea (4 subjects [2.0%]), upper abdominal pain (3 subjects [1.5%]), and nausea (3 subjects [1.5%]).

Common Adverse Events

The most common events were in the infections and infestations (18.4%) and gastrointestinal disorders (18.0%) system organ classes (SOCs). TEAEs in the combined diclofenac groups (54.0%) occurred more frequently than in the placebo group (44.7%) and a dose-related

trend was evident between the tid and bid treatment groups. Nausea was the most frequently reported TEAE in the combined diclofenac groups (14 subjects [6.9%]), followed by diarrhea (12 subjects [5.9%]).

Trial DIC3-08-06

"A Multicenter, Open-Label, Safety Trial of Diclofenac Nanoformulation Capsules 35 mg in Subjects With Osteoarthritis of the Knee or Hip"

Conducted from 1/9/2012 to 3/27/2013.

This was a multicenter trial conducted at 40 sites in the US.

Overview
This was a Phase 3, multicenter, open-label trial to evaluate the safety of diclofenac for up to 52 weeks in patients with OA of the knee or hip. As communicated during a Type B end-of-Phase 2 meeting with the Applicant on 11/9/2010, the safety database requirement must include ≥ 300 patients treated ≥6 months and ≥100 patients treated ≥ 1 year. Given diclofenac has been on the market for many years the required safety database in less than drugs with less exposure. This is a brief review of the primary analysis of efficacy and safety data from this study.

Protocol
Key Inclusion Criteria:

- Male or female ≥40 years of age
- Diagnosis of OA of the hip or knee with ongoing knee and/or articular hip pain
- Current chronic user of NSAIDs and/or acetaminophen for his/her OA pain and was anticipated to benefit from continuous treatment with therapeutic doses of NSAIDs[12]
- Body weight ≥45 kg and a body mass index (BMI) ≤40 kg/m^2
- Nonlactating and nonpregnant[13]
- If female, was either not of childbearing potential or was practicing medically acceptable methods of birth control and agreed to continue with the regimen throughout the trial[14]
- Ambulatory

Key Exclusion Criteria:

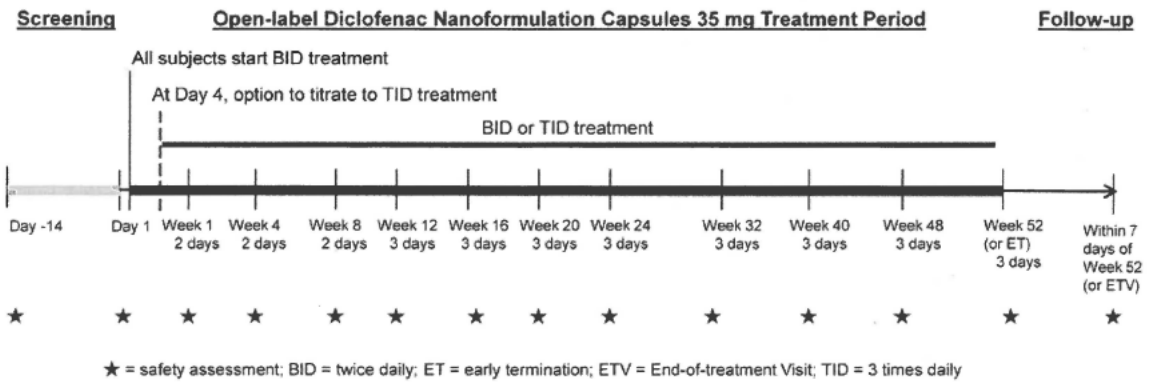
- History of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any NSAIDs; history of NSAID-induced bronchospasm; or hypersensitivity, allergy, or significant reaction to any ingredients of the trial drug
- Required chronic use of opioid or opioid combination products
- Had any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the Investigator, could compromise the subject's welfare

[12] A current chronic user was defined as a subject who had used these treatments for ≥20 days of the last 30 days before Screening
[13] Negative serum pregnancy test result at Screening and a negative urine pregnancy test result at Baseline
[14] Hormonal methods such as oral, implantable, injectable, or transdermal; Total abstinence; Intrauterine device; Double-barrier method

- History or current diagnosis of a significant psychiatric disorder that, in the opinion of the Investigator, would affect the subject's ability to comply with the trial
- Diagnosed with cancer within 5 years before Screening
- Known or suspected history of alcoholism or drug abuse or misuse within 2 years before Screening or evidence of tolerance or physical dependence
- History of a clinically significant (Investigator opinion) GI event within the 6 months before Screening or had any history of peptic or gastric ulcers or GI bleeding
- Had a surgical or medical condition of the GI or renal system that might have significantly altered the absorption, distribution, or excretion of any drug
- Had received hyaluronic acid injections in the target joint in the 6 months before Screening or between Screening and Baseline
- Had received systemic corticosteroids (either oral or parenteral) within 3 months before Screening
- Had used aspirin or aspirin-containing products within 7 days before trial drug. Aspirin at a daily dose of ≤325 mg/day was allowed for cardiovascular prophylaxis if the subject had been on a stable dose regimen for ≥30 days
- Receiving or expected to use anticoagulants
- Had started physical therapy within 4 weeks before Screening. Subjects who had at least 4 weeks of physical therapy (allowing time to stabilize on treatment) and were planning to remain on a stable regimen throughout the treatment were not excluded
- Was a candidate for imminent (i.e., during the 5 months after Screening) joint replacement
- Tested positive either on the urine drug screen or on the alcohol breathalyzer test
- Had a significant renal or hepatic disease, as indicated by laboratory assessment (results ≥3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase, or creatinine ≥1.5 times the ULN) or had any significant laboratory finding that in the Investigator's opinion contraindicates trial participation
- Difficulties swallowing capsules or was unable to tolerate oral medication

Subjects were to undergo screening within 2 weeks prior to treatment (Day 1). The open-label treatment phase was to be 52 weeks and the final trial assessment occurred at the Follow-up visit, about 1 week after the final dose (Figure 6). Subjects were to be recruited independently from DIC3-08-05 or continue from DIC3-08-05. For subjects who completed the DIC3-08-05 trial, applicable demographic and medical history data and Week 12 assessments from that trial were used in lieu of a screening visit for this trial. All subjects began treatment with diclofenac 35 mg bid. Four days following the start of dosing, a subject's dose could be titrated to diclofenac 35 mg tid provided the subject was tolerating trial drug with no unacceptable AEs and both the investigator and subject agreed that the dose should be increased. As detailed in Section 7, the Applicant was to collect exposure data for both dosing groups given titration was allowed (i.e., number of days/months exposed to TID dose). This is of importance given the tid dose showed efficacy in the pivotal trial DIC3-08-05 and therefore would likely be the marketed dose. For details of the study schedule refer to Table 20.

Figure 6: Study Design



★ = safety assessment; BID = twice daily; ET = early termination; ETV = End-of-treatment Visit; TID = 3 times daily

Note: Subjects were newly enrolled or rollover subjects from trial DIC3-08-05 who received Diclofenac Nanoformulation Capsules 35 mg tid, 35 mg bid, or placebo for 12 weeks. Subjects who rolled over from trial DIC3-08-05 must have completed the 12-week trial period.

Source: Applicant's Study Report, DIC3-08-06, p. 25

Treatments

- Subjects were to receive either diclofenac 35 mg BID or TID. The dose could be titrated up or down during the trial.
- Acetaminophen, up to 500 mg administered every 4 to 6 hours as needed (maximum of 3,000 mg per day) was permitted as rescue medication.

Table 20: Study Schedule

	Screening	Treatment Period[b]						Follow-up
	Screening Visit (Days -14 to -1)[a]	Baseline Day 1	Week 1, 4 and 8 ± 2 days	Week 12 ± 3 days	Week 16 and 20 ± 3 days	Week 24, 32, 40, and 48 ± 3 days	Week 52/ET ± 3 days	Within 7 days of Week 52/ET ± 3 days
Written informed consent	X							
Assign subject identification number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X	X[c,d]						
Physical examination	X	X[c,e]					X[e]	
Vital signs[f]	X	X[c]	X	X	X	X	X	X
Height, weight, and BMI	X							
12-lead ECG	X						X	
Clinical laboratory tests (hematology, chemistry, urinalysis)	X[f]		X[g]	X		X	X	
Pregnancy test for female subjects of childbearing potential[h]	X	X[c]		X		X	X	
Urine drug screen	X	X[c]						
Alcohol breathalyzer test	X	X[c]						
Health Survey (SF-36v2)	X	X		X		X	X	
Dispense trial drug		X	X	X	X	X		

	Screening	Treatment Period[b]						Follow-up
	Screening Visit (Days -14 to -1)[a]	Baseline Day 1	Week 1, 4 and 8 ± 2 days	Week 12 ± 3 days	Week 16 and 20 ± 3 days	Week 24, 32, 40, and 48 ± 3 days	Week 52/ET ± 3 days	Within 7 days of Week 52/ET ± 3 days
Collect trial drug and perform accountability		X	X	X	X	X	X	
Concomitant medications	X	X[c]	X	X	X	X	X	X
Adverse events		X[c]	X	X	X	X	X	X
Review procedures/schedule visit	X	X	X	X	X	X	X	

Abbreviations: BMI = body mass index; ECG = electrocardiogram; ET = early termination; SF-36v2 = Short Form-36 Health Survey, Version 2

[a] Screening assessments were performed within 14 days before the Baseline Visit (Day 1) and were completed before administration of the first dose of trial drug. For subjects who rolled over from the DIC3-08-05 trial, applicable demographic and medical history data and Week 12/ET assessments from that trial were used in lieu of a Screening Visit for this trial.

[b] Week 1, 4, and 8 Visits were scheduled with windows of ± 2 days; Week 12, 16, 20, 24, 32, 40, 48, 52, and Follow-up Visits were scheduled with windows of ± 3 days.

[c] Was performed before the first dose of trial drug was administered.

[d] Medical history since Screening was updated.

[e] A complete physical examination (excluding the genitourinary examination) was performed at Screening. An abbreviated physical examination (excluding the genitourinary examination) assessing changes from the initial physical examination was performed at Baseline (Day 1) and Week 52/ET visits.

[f] Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature were measured after the subject had been in a sitting position for 5 minutes.

[g] At Week 4 and Week 8 Visits only.

[h] Serum pregnancy test at Screening and urine pregnancy test at all other specified time points. Test results must have been negative for the subject to continue in the trial.

Source: Applicant's Study Report, DIC3-08-06, p. 33

Efficacy
Efficacy was not formally assessed in this trial.

Safety

- A total of 601 subjects received at least one dose of open-label treatment with diclofenac 35 mg BID. Of these, 302 subjects were uptitrated to diclofenac 35 mg TID at least once during the trial (see Section 7 for detailed exposure and safety analysis).
- Serious adverse events were reported in 42 subjects (7.0%) overall with the percentage of subjects reporting SAEs was similar between the 2 dosing regimens (4.3% for BID compared to 5% for TID group)
- The most commonly reported event was osteoarthritis, which was reported by 3 subjects (0.5%)
- One subject met the criteria for Hy's Law in the tid group and is described in Section 7
- AEs were reported by a slightly higher percentage of subjects while receiving the tid dosing regimen (61.6% of subjects) compared with the BID dosing regimen (56.6% of subjects)
- The highest proportion of subjects and most frequent events, overall, were: upper respiratory tract infection (47 subjects [7.8%]; 53 events), headache (46 subjects [7.7%]; 71 events), and urinary tract infection (44 subjects [7.3%]; 50 events).
    - AEs occurred mostly at similar rates between groups

Conclusion

- The results of this trial serve as supportive evidence of safety in a group of subjects exposed to diclofenac for an extended period of time
- The number of subjects exposed and the duration of exposure is acceptable given the already established safety of diclofenac
- There were no new safety signals identified. One case of Hy's law was identified, however diclofenac already has information regarding severe liver injury within the existing product labeling

6 Review of Efficacy

Efficacy Summary

Based on the review of a pivotal Phase 3 trial (DIC3-08-05) there is evidence of efficacy for the 35 mg tid treatment group for the treatment of osteoarthritis pain in adults. The Applicant seeks an indication of treatment of osteoarthritis pain. For inclusion into the trial, patients must have had a minimum VAS pain score of 40mm and an increase of ≥ 15 mm between screening and the baseline visit. The analyses of the primary endpoint were statistically significant in favor of diclofenac 35 mg tid treatment group but not the bid treatment group. Although the BID did not reach statistical significance in the primary analysis, there was a trend towards a treatment effect. A sensitivity analysis was also performed and supported the findings of efficacy. Secondary endpoints, such as the PGIC and WOMAC Function Subscale, also provided supportive evidence of efficacy for the tid treatment group with less compelling support for the bid treatment group. No secondary endpoints were identified as key endpoints and they Applicant did not control for multiplicity. Therefore, the proposed indication of treatment of osteoarthritis pain is appropriate, as opposed to treatment of the

signs and symptoms of osteoarthritis. To obtain the indication for the treatment of signs and symptoms of osteoarthritis an Applicant must demonstrate efficacy using three primary endpoints with an analysis of the mean changes from baseline in pain, function and patient global with appropriate statistical methods to address the multiple endpoints.

The prespecified primary endpoint for the clinical trial DIC3-08-05 was the change in WOMAC pain subscale from baseline to Week 12. The Applicant submitted an sNDA for their proposed indication to their Zorvolex NDA recently approved for treatment of acute pain. The Division agreed the Applicant may perform a single well-controlled pivotal Phase 3 trial to support their application using the change in the WOMAC pain subscale at 12 week in patients with osteoarthritis of the hip or knee as the primary endpoint for efficacy.

Since this application is supported by one pivotal Phase 3 clinical trial (DIC3-08-05), much of the information with regard to efficacy is described in detail in Section 5.3. Section 6 will discuss the statistical reviewer's confirmatory and additional analyses and provide a high-level summary of the key findings.

The Applicant hypothesized that their formulation of diclofenac would show increased dissolution and absorption rates leading to comparable efficacy at a lower dose and a possible improved safety profile compared to the reference drug. However, none of the efficacy studies included the reference drug, Cataflam, therefore, no comparative conclusion can be made with regard to efficacy or safety between the Applicant's drug and the reference drug.

6.1 Indication

The proposed indication is for the treatment of osteoarthritis pain. As discussed above, and in previous meetings between the Applicant and the Division, the study design and endpoints are appropriate for the proposed indication.

6.1.1 Methods

See Section 5.3.

6.1.2 Demographics

See Section 5.3.

6.1.3 Subject Disposition

See Section 5.3.

6.1.4 Analysis of Primary Endpoint(s)

The Applicant's pre-specified primary efficacy endpoint for trial DIC3-08-05 was the mean change from baseline in the WOMAC pain subscale score at Week 12 or early termination. The WOMAC pain subscale score consists of five questions regarding pain during walking, using the stairs, in bed, sitting or lying, and standing. Each question is answered on a 100 mm VAS scale with 0 being no pain and 100 the worst possible pain. The 12 week WOMAC pain subscale score was the agreed upon primary endpoint discussed in numerous meetings with the Applicant and the Division during the clinical development process. The WOMAC pain subscale measure at 12 weeks is the Division's preferred assessment of osteoarthritis pain.

There was concern regarding the method of assessing missing data using the mixed model repeated measures analysis (MMRM) and this was discussed with the Applicant under a special protocol assessment. Our statistician, Mr. David Petullo, noted in his review "Concerns noted were the mixed model repeated measures analysis (MMRM) which assumes that missing data is missing at random." There was also a concern noted with how rescue medication would be handled in the primary analysis. The applicant proposed to use LOCF for the WOMAC pain subscale score for patients who took rescue medication within 12 hours of a scheduled study visit. However, the last observation may not represent the pain level necessitating the use of rescue. Thus, we recommended the applicant assess the pain score just prior to taking rescue medication and use that score for the following study visit."

The Applicant's analyses of efficacy showed superiority of the diclofenac tid treatment group, but not the bid group, when compared to placebo. Mr. David Petullo confirmed the Applicant's results and provided a summary of the primary analyses (Table 20). All analyses account for missing pain scores and use of rescue medication. Mr. Petullo's analyses consistently showed a significant treatment effect observed for the TID dose as well as the lack of significance for the BID dose group (Table 21).

Table 21: Results from analysis of primary endpoint

Analysis	Imputation	Mean change from baseline pain at Week 12 (stdev)		
		placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
MMRM	none	35.0 (2.9)	41.7(2.8)	46.6 (3.0)*
ANCOVA	BOCF	28.9 (3.2)	36.4 (3.2)	39.3 (3.4)*
ANCOVA	BOCF/LOCF	30.4 (3.2)	38.3 (3.2)	40.1 (3.4)*
ANCOVA	return to BL	28.7 (3.2)	36.4 (3.3)	40.3 (3.5)*

* p-value for comparison to placebo < 0.05

Source: David Petullo's Statistical Review, Table-3

In Mr. David Petullo's analysis, if a subject used rescue medication within 12 hours of scheduled study visit, he randomly assigned a score from the distribution of baseline scores and used this in the analysis. However, there were very few subjects that required rescue medication within 12 hours of a study visit (Table 22). Hence, it may be concluded that use of rescue medication did not influence the primary analysis.

Table 22: Number of subjects that used of rescue medication within 12 hours of a scheduled study visit

Visit	Number of subjects , n		
	placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
Week 2	0	1	2
Week 6	3	3	1
Week 12	2	1	3
Over-all	5	5	6

Source: David Petullo's Statistical Review, Table-4

When no imputation of missing data was analyzed, Mr. Petullo noted there was a decrease in the WOMAC pain subscale score at each visit (Table 23).

Table 23: Mean WOMAC pain subscale scores by visit

		Visit			
Treatment	statistic	Baseline	Week 2	Week 6	Week 12
Placebo	mean	76.1	52.8	44.1	42.2
	95% CI	[72.9, 79.2]	[47.4, 58.2]	[38.5, 49.6]	[36.4, 48.0]
	n	103	92	87	86
Zorvolex 35 mg BID	mean	74.7	43.1	36.1	32.7
	95% CI	[72.0, 77.4]	[38.2, 48.2]	[30.5, 41.6]	[26.9, 38.4]
	n	103*	100	91	89
Zorvolex 35 mg TID	mean	77.0	38.8	31.7	29.3
	95% CI	[74.2, 79.8]	[33.3, 44.2]	[26.6, 36.8]	[24.1, 34.4]
	n	98	94	86	82

*One subject missing baseline pain score

Source: David Petullo's Statistical Review, Table-6

Additional sensitivity analyses were performed by the Applicant. These analyses included graphical assessment of WOMAC pain subscale scores for dropouts, an MMRM analysis where dropouts were penalized, ANCOVA with baseline observation carried forward (BOCF) and last observation carried forward (LOCF), and multiple imputation using a pattern mixture framework. Overall missing data was fairly low. The results of this sensitivity analysis were consistent with those of the primary analysis. For details regarding the statistical methodologies please refer to Mr. David Petullo's statistical review.

My interpretation of the results is consistent with Mr. Petullo's final conclusion. The Applicant has adequately demonstrated, based on the primary and sensitivity analyses, that the diclofenac 35 mg TID dose has a clinically significant impact in the treatment of osteoarthritis pain. However, the BID diclofenac group failed to show a substantial improvement. Therefore, I recommend the approved dose for the indication of treatment of osteoarthritis pain should be 35 mg three times per day.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints included PGIC, function subscale of the WOMAC (post-hoc analysis performed by the Applicant), amount of rescue medication consumed, and the percentage of subjects that achieved at least a 30% and 50% reduction in baseline pain. The Applicant performed numerous analyses discussed in Section 5 and generally the tid group showed a significant difference from placebo. These secondary outcome measures provide supportive evidence of efficacy for the treatment of osteoarthritis pain. The Applicant did not control for multiplicity nor identify any of the secondary outcomes as key. As discussed in a special protocol assessment, the study design would only be applicable to treating osteoarthritis pain and not the signs and symptoms of osteoarthritis. Mr. Petullo performed additional analyses confirming some of the secondary outcome measures reviewed below.

Mr. Petullo examined the percentage of subjects that achieved at least a 30% and at least a 50% improvement from their baseline pain score at Week12. If a subject discontinued treatment prior to Week 12 they were considered non-responders. Both cases showed that more subjects in the diclofenac treatment groups achieved at least a 30% improvement and 50% improvement compared to placebo. However, only the TID dose showed the difference from placebo was statistically significant (Table 24).

Table 24: Percentage of subjects achieving at least a 30% or 50% improvement

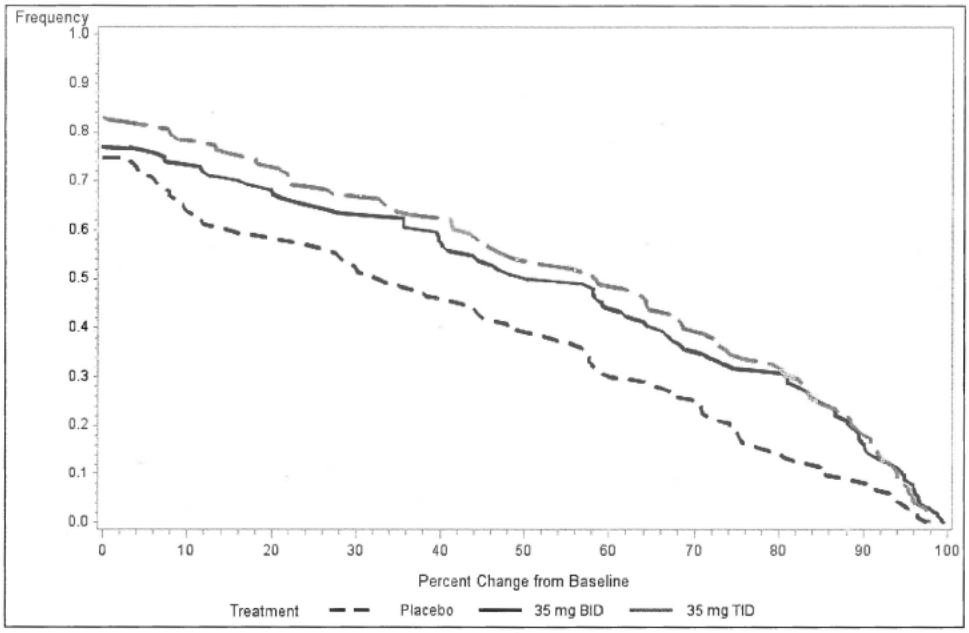
treatment	Percent Improvement from Baseline, % of subjects	
	30%	50%
placebo	52.4	39.8
Zorvolex – BID	63.5	51.0
Zorvolex – TID	67.4*	54.1*

* p-value < 0.05

Source: David Petullo's Statistical Review, Table-7

Mr. Petullo also examined cumulative responder curves for each treatment group. Those that did not complete the study were considered non-responders. There was clear separation between both doses of diclofenac and placebo at all response levels (Figure 7).

Figure 7: Cumulative responder curves



Source: David Petullo's Statistical Review, Figure 1

Mr. Petullo's analysis of the change from baseline in the WOMAC composite scores at Week 12, displayed in Table 25, showed both treatment groups were significantly different from placebo (WOMAC Composite scores - change from baseline).

Table 25: WOMAC Composite scores - change from baseline

Treatment	Change from baseline at Week 12		
	LSMEAN	95% CI	Diff from placebo
Placebo	26.1	[20.2, 31.9]	-
Zorvolex – BID	33.8	[27.9, 39.6]	7.7*
Zorvolex – TID	35.6	[29.3, 41.8]	9.5*

*p-value < 0.05

Source: David Petullo's Statistical Review, Table-9

With regard to PGIC scores Mr. Petullo considered scores of 1,2, or 3 (very much improved, much improved, or minimally improved a success. His analysis showed statistical significance for both treatment groups (Table 26).

Table 26: Comparison of PGIC scores

treatment	% Responders
placebo	56
Zorvolex – BID	73*
Zorvolex – TID	74*

* p-value < 0.01
Source: David Petullo's Statistical Review, Table-10

6.1.7 Subpopulations

The Applicant examined the primary efficacy endpoint, difference in WOMAC Pain subscale scale between baseline and Week 12, for differences due to age or gender. Age was categorized as less than 65 years old or 65 years or older. Mr. Petullo analyzed the primary endpoint by subpopulations including gender, age, and race for all the randomized subjects. Mr. Petullo utilized an ANCOVA model with an interaction term for each subgroup. As expected the effect of treatment was consistent for age, gender, and racial subgroups. Mr. Petullo also examined the treatment effect for any differences due to site location. As with the other subgroups, the effect of treatment was consistent for sites.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Diclofenac was evaluated at 35 mg BID and TID in one adequate and well-controlled trial. Only the TID dosing showed statistical significance compared to placebo in the primary analysis. These findings were confirmed by Mr. Petullo and the sensitivity analyses performed by the Applicant. There was a trend towards significance for the bid treatment group, but regardless of analysis, this group did not reach statistical significance. There were supportive findings in both treatment groups through the secondary analyses as well. In general, the secondary outcome measures seemed to favor the TID group when compared to the BID group. Therefore, I recommend only the diclofenac 35 mg TID dose be approved for the proposed indication in this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Applicant performed numerous analyses based on assessments at 2, 6 and 12 weeks or early termination. There does appear to be any evidence of tolerance to the drug with regard to efficacy for

treatment of osteoarthritis pain. Additionally, efficacy appears to increase with time up to 12 weeks as measured by the WOMAC pain subscale at various time points (e.g., Table 23).

6.1.10 Additional Efficacy Issues/Analyses

The Applicant did not design the study to show a direct comparison in efficacy between the diclofenac groups and another active comparator. Therefore, comparative claims cannot be made between the Applicant's product and another active drug (e.g., Cataflam).

7 Review of Safety

Safety Summary

The safety profile of diclofenac capsules, for the indication of osteoarthritis pain, was assessed in two clinical trials (DIC3-08-05 and DIC3-08-06). For the placebo-controlled trial DIC3-08-05, diclofenac was dosed in two groups of either twice or three times per day. In the open-label safety trial DIC3-08-06, patients received flexible diclofenac dosing of either 35 mg twice per day or three times per day. Given the drug is intended for a population with a chronic condition, patients were exposed to the drug for an extended period of time during the safety study DIC3-08-06. During the end of Phase 2 meeting with the Applicant, the Division informed the Applicant the safety database should consist of approximately 300 patients treated for at least 6 months and approximately 100 patients for at least 1 year duration. A total of 766 unique patients were enrolled in the two trials. No new significant safety concerns were identified for diclofenac in general or that were unique to diclofenac capsules. There is a dose-related trend for AEs in the integrated population, with TEAEs higher in the three times daily dosing regimen (64.3 % of subjects) compared with the twice daily dosing regimen (57.7%). However, in the 52-week safety study completion rates were higher in the three times daily (72%) compared to overall population (59.8%) at ≥6 continuous months exposure. This would suggest tolerability is not a major factor in adherence and patients may have shown an improved benefit of treatment in this group.

The Applicant submitted a supplement application to NDA 204592. The information available within this application appears adequate to assess the safety of diclofenac capsules in the osteoarthritis population in conjunction with the established safety profile for diclofenac. The Applicant's rationale for their formulation of diclofenac is based on their hypothesis that the increased dissolution and absorption due to particle size may allow less drug product to be used and therefore an improved safety profile over Cataflam. There is no head-to-head trial with the reference drug, Cataflam, or any other NSAID. Therefore, no comparative conclusion can be made with regard to safety between the Applicant's drug and the reference drug or other NSAIDs. The information below discusses both the controlled trial (DIC3-08-05) and the 52-week safety study (DIC3-08-06). Some sections combine the trials (e.g., total exposure), but where applicable I discussed the trials separately.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

One controlled trial and one uncontrolled, open-label trial conducted in the osteoarthritis population were submitted in support of this supplemental NDA. Refer to Section 5.3 for a description of the trials. A safety analysis was performed on each trial, DIC3-08-05 (12-week trial) and DIC3-08-06 (52-week trial) as well as pooling the safety population, by reviewing treatment-emergent AEs (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, TEAEs of special interest, physical examination, clinical laboratory tests, vital signs, and 12-lead electrocardiogram (ECGs).

Trial DIC3-08-05 was a controlled-trial conducted in the United States which consisted of 305 patients who were randomized and 258 patients completed the trial.

Trial DIC3-08-06, 602 patients were enrolled and 360 patients completed the 52-week trial.

Overall, the integrated safety population consisted of 705 patients who received at least 1 dose of either 35 mg twice or three times per day.

Deleted Sections

- No data was submitted to inform a discussion of Sub-sections 7.2.3 Special Animal and/or In Vitro Testing and 7.2.5 Metabolic, Clearance, and Interaction Workup, 7.4.2 Laboratory Findings, 7.4.4 Electrocardiograms (ECGs), were 7.4.6 Immunogenicity, 7.5.4 Drug-Disease Interactions, 7.5.5 Drug-Drug Interactions, 7.6.1 Human Carcinogenicity, 7.6.2 Human Reproduction and Pregnancy Data, and these sections were deleted
- Sub-sections 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class was not relevant and was deleted
- Subsection 7.3.5 was deleted because there are no submission specific primary safety concerns to discuss
- Subsection 7.4.5 Special Safety Studies/Clinical Trials was deleted because there were no special safety studies performed
- 7.5.4 Drug-Disease Interactions, 7.5.5 Drug-Drug Interactions were not studied in this application and were deleted
- No data was submitted to sub-sections 7.6.1 Human Carcinogenicity, 7.6.2 Human Reproduction and Pregnancy Data and were deleted

7.1.2 Categorization of Adverse Events

All treatment emergent adverse events (TEAEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.0. Individual AEs by system organ class (SOC) and preferred term (PT) were summarized for subjects in each treatment group and overall by number and percentage of subjects, severity, and relationship to trial drug. Each subject was counted only once for each PT. If a subject experienced more than 1 AE with the same preferred term, only the AE

with the strongest relationship or the greatest severity was included in the summaries of relationship and severity.

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

Safety data was pooled from trials DIC3-08-05 and DIC3-08-06. Patients could rollover from trial DIC3-08-05 into trial DIC3-08-06 and subjects in DIC3-08-06 were allowed to switch dosing regimens. The following groups were defined as subsets for the integrated safety population disposition, demographics and baseline characteristics:

- **Zorvolex Capsules 35 mg bid**: data from patients randomized to twice daily dosing in DIC3-08-05 or who completed safety assessments at any time whole receiving Zorvolex twice daily in DIC3-08-06
- **Zorvolex Capsules 35 mg tid**: data from patients randomized to three times daily treatment in trial DIC3-08-05 or who completed safety assessments at any time while receiving Zorvolex three times daily in DIC3-08-06
- **Zorvolex Capsules 35 mg bid/tid:** data from all patients in trial DIC3-08-06
- **Combined Zorvolex Capsules**: data from patients who received diclofenac twice daily or three times daily treatment in either trial
- **Placebo**: patients who rolled-over from trial DIC3-08-05, data was pooled across the trials, but the subject was counted only once in this category
- **Total:** patients who received trial drug in either trial

For TEAEs and concomitant medication assessments, the following groups were defined for the Integrated Safety Population:

- **Zorvolex Capsules 35 mg bid**: data from patients with a safety assessment or who received medication while randomized to twice daily treatment in trial DIC3-08-05 or were receiving twice daily treatment in trial DIC3-08-06 at the time of the assessment
- **Zorvolex Capsules 35 mg tid**: data from patients with a safety assessment or who received medication while randomized to three times daily treatment in trial DIC3-08-05 or were receiving three times daily treatment in trial DIC3-08-06 at the time of the assessment
- **Combined Zorvolex Capsules**: data from all patients who received diclofenac twice daily or three times daily treatment in either trial For subjects who rolled-over from trial DIC3-08-05, data was pooled across the trials, but the subject was counted only once in this category.
- **Placebo**: data from subjects randomized to placebo treatment in trial DIC3-08-05 only
- **Total:** data from all patients who received trial drug in either trial (i.e., Zorvolex Capsules 35 mg three times daily, twice daily, or placebo).

7.2 Adequacy of Safety Assessments

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

Exposure

For the controlled trial, DIC3-08-05, a total of 202 patients received diclofenac. In the uncontrolled trial, DIC3-08-06, a total of 601 patients received at least one dose of open-label treatment with diclofenac. Of these, 302 subjects uptitrated to diclofenac 35 mg three times daily at least once during the trial. The controlled trial was allowed to rollover into the open-label trial and provided a total of 705 unique exposures. The Division informed the Applicant, during the End of Phase 2 meeting, a safety database should contain approximately 300 subjects treated for at least 6 months and approximately 100 patients treated for at least 1 year for an osteoarthritis pain indication at the efficacious dose. Greater than eleven months is considered the full trial since the first two weeks were a mandatory period of twice per day dosing. As shown in Table 27, the efficacious dose (three times per day) shows exposure for at least 6 months (N=161) and 11 months (n=83) is less than the suggested database. However, the safety database provided is adequate given the known safety profile of diclofenac, the total exposure (BID and TID) of diclofenac well exceeds the required database, and the cmax for this drug is less than the reference drug Cataflam (osteoarthritis the recommended dosage is 100-150 mg/day in divided doses). In addition, patients did not titrate down very often from three times daily to twice daily dosing. Note in Table 27, the overall exposure and continuous exposures were nearly identical for the TID dosing. This suggests that the higher dose was well tolerated and provides additional support for overall safety.

Table 27: Summary of Duration on Trial Drug by Months – DIC3-08-06 Safety Population

	Diclofenac Nanoformulation Capsules		
Exposure Type	35 mg bid N=601	35 mg tid N=302	Combined N=601
Overall exposure by months, number of subjects (%)			
≥3 months	328 (54.6)	209 (69.2)	513 (85.4)
≥6 months	252 (41.9)	161 (53.3)	426 (70.9)
≥9 months	227 (37.8)	120 (39.7)	394 (65.6)
≥10 months	208 (34.6)	100 (33.1)	376 (62.6)
≥11 months	200 (33.3)	83 (27.5)	373 (62.1)
≥12 months	122 (20.3)	4 (1.3)	268 (44.6)
Longest continuous exposure[a] by months, number of subjects (%)			
≥3 months	325 (54.1)	208 (68.9)	--
≥6 months	248 (41.3)	160 (53.0)	--
≥9 months	220 (36.6)	117 (38.7)	--
≥10 months	200 (33.3)	100 (33.1)	--
≥11 months	190 (31.6)	83 (27.5)	--
≥12 months	123 (20.5)	4 (1.3)	--

Source: DIC3-08-06 Clinical Study Report p. 73

Demographics

The safety population in both trials consisted of patients with a mean age near 60 years old (mean 60.2), predominately women (62.1%), and white (83%). Demographic information is reviewed in more detail in Section 5.3 under each individual trial.

7.2.2 Explorations for Dose Response

There was no formal analysis for testing a dose response with regard to safety. I did not note any clear evidence of a safety concern related to the difference between the two dosing regimens in the data presented.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trial in Section 5.3, which appears adequate for this population.

7.3 Major Safety Results

Within this section a greater emphasis is placed on the controlled trial data (DIC3-08-05) given there is a placebo control group for comparison.

7.3.1 Deaths

No deaths were reported in trial DIC3-08-05 or DIC3-08-06.

7.3.2 Nonfatal Serious Adverse Events

Trial DIC3-08-05:

Serious adverse events (SAE) were reported in 9 patients (3.0%) in the controlled trial DIC3-08-05. The SAEs break down in the following manner: 4 subjects (4.1%) in the diclofenac 35 mg three times daily group, 3 subjects (2.9%) in the diclofenac 35 mg twice daily group, and 2 subjects (1.9%) in the placebo group. A summary of the SAEs are provided below (Table 28). No SAE occurred in more than one subject. No trend in SAE type or frequency was identified between groups. As shown in the table below, there were no serious CV or renal TEAEs during the trial.

Table 28: Summary of SAEs by Preferred Term – DIC3-08-05 Safety Population

Preferred Term, n (%)	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	35 mg tid n=98	Combined n=202	Total n=305
Subjects with ≥1 SAE[a]	2 (1.9)	3 (2.9)	4 (4.1)	7 (3.5)	9 (3.0)
Alanine aminotransferase increased	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Appendicitis	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Aspartase aminotransferase increased	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Chronic obstructive pulmonary disease	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Deep vein thrombosis	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Hepatic cancer metastatic	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Malignant melanoma	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Metastases to lung	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Metastatic neoplasm	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Non-cardiac chest pain	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Pulmonary embolism	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Hemiplegic migraine	1 (1.0)	0	0	0	1 (0.3)
Syncope	1 (1.0)	0	0	0	1 (0.3)

Source: Section 14.3.2. Post-hoc Table 14.3.1.8.1

Abbreviations: AE = adverse events; bid = twice daily; TEAE =treatment-emergent adverse event; tid=3 times daily

Note: The denominator for the percentages was the number of subjects in each treatment group. At each level of summarization (system organ class or preferred term), subjects experiencing more than 1 TEAE were counted only once. All TEAEs were coded by using the Medical Dictionary for Regulatory Activities, Version 14.0.

[a] Treatment-emergent AEs were defined as AEs with an onset at the time of or following the start of treatment with trial drug or AEs that started before the start of treatment but increased in severity or relationship at the time of or following the start of treatment.

Source: Applicant CSR p.122

I reviewed the SAE narratives, and the events related to the study drug are all consistent with the known safety profile of diclofenac. Certain adverse events (AEs) (i.e., aminotransferase elevation, hypertension) are previously known AEs associated with diclofenac and there was no concerning increase in frequency of these events categorized under SAEs. A case of non-cardiac chest pain also occurred in the diclofenac TID group. The chest pain did occur following 30 days of exposure to

diclofenac, however, the patient had risk factors for cardiac disease and ultimately the diagnosis was determined to not be of cardiac origin. A cause and effect was not established.

Other SAEs listed above do not appear to have a relationship with the use of diclofenac. The case of appendicitis occurred after completion of the trial dosing period. The SAE involving hepatic cancer and melanoma are likely unrelated given the length of exposure to the drug and the patient population is within an age group where malignancies are more prominent. One subject developed a deep venous thrombosis and subsequent pulmonary embolism. This subject also had fractured her wrist and ankle and suffered a knee injury, leaving the subject immobile two weeks prior to the event.

Overall, after a review of the SAEs and case narratives in the trial, there was no identifiable trend in type or frequency of the events between groups. No new safety signal was identified for diclofenac.

Trial DIC3-08-06

Serious adverse events (SAE) were reported in 42 subjects (7.0%) in the open-label safety trial DIC3-08-06. There was no placebo group in this trial, therefore, only a comparison between diclofenac 35 mg BID and 35 mg TID can be made. The percentages of SAEs, and frequencies of the type of SAEs, were similar between dosing regimens. The most commonly reported event was osteoarthritis, which was reported by 3 subjects (0.5%) when combining the dosing groups. No other SAE occurred in more than 2 subjects. There were a total of 8 cardiovascular events; myocardial infarction (n=2), unstable angina (n=1), angina; pectoris (n=1), carotid artery stenosis (n= 3), and coronary artery disease (n=3). No clear relationship was identified between dosing groups. Assessment of cardiac disorders were confounded by the age and comorbidity of the population. In addition, the follow-up period is lengthy (52 weeks), and provides an extensive time period for this population to develop a number of disorders which may or may not be related to the treatment. A review of the case summaries showed these subjects had risk factors for cardiovascular disorders, and therefore a relationship to diclofenac treatment could not be identified. I reviewed the case summaries submitted by the Applicant for all SAEs and no new safety signal was identified for diclofenac.

When combining both studies, SAEs were uncommon in the integrated safety population (Table 29). The events are discussed above in their respective studies. The pooled safety population did not reveal any new safety signals for diclofenac.

Table 29: SAEs Occurring in >1 Subject by Preferred Term - Integrated Safety Population

Preferred Term	Zorvolex Capsules 35 mg tid[a] N=373 n (%)	Zorvolex Capsules 35 mg bid[b] N=655 n (%)	Combined Zorvolex Capsules 35 mg[c] N=705 n (%)
Any SAE	19 (5.1)	29 (4.4)	48 (6.8)
Chronic obstructive pulmonary disease	0	3 (0.5)	3 (0.4)
Osteoarthritis	1 (0.3)	2 (0.3)	3 (0.4)
Carotid artery stenosis	0	2 (0.3)	2 (0.3)
Chest pain	0	2 (0.3)	2 (0.3)
Diverticulitis	1 (0.3)	1 (0.2)	2 (0.3)
Lumbar spinal stenosis	1 (0.3)	1 (0.2)	2 (0.3)
Myocardial infarction	0	2 (0.3)	2 (0.3)
Pulmonary embolism	2 (0.5)	0	2 (0.3)

Source: 5.3.5.3 Integrated Summary of Safety, Table 14.3.2.2.2

Source: Applicant Summary of Clinical Safety p.54

7.3.3 Dropouts and/or Discontinuations

Trial DIC3-08-05

A total of 47 subjects (15.4%) withdrew for any reason. Withdrawals due to lack of efficacy was uncommon; 2 subjects withdrew due to lack of efficacy in the diclofenac BID group and 6 subjects discontinued due to lack of efficacy in the placebo group. Twenty-five subjects (8.2%) withdrew due to an AE. The most common reason for withdrawal was due to gastrointestinal events (n=10) and these were only seen in the diclofenac groups (Table 30). I reviewed through the individual case reports for subjects who withdrew due to a TEAE and summary analysis provided by the Applicant. I determined that although there is a trend towards increased number of withdrawals due to a TEAE for the diclofenac groups, with a slight increase in the TID group, the overall number of withdrawals were relatively small and represent known adverse events associated with diclofenac.

I also reviewed the case summaries for subjects who discontinued due to a withdrawal of consent. It is my determination that these subjects did not withdraw due to any AE related to the drug product.

Table 30: Summary of TEAEs Leading to Trial Discontinuation in at Least 2 Subjects in any Treatment Group by Preferred Term – Safety Population DIC3-08-05

Preferred Term, n (%)	Placebo n=103	Diclofenac Nanoformulation Capsules			Total n=305
		35 mg bid n=104	35 mg tid n=98	Combined n=202	
Any TEAE leading to trial discontinuation[a]	4 (3.9%)	9 (8.7%)	12 (12.2%)	21 (10.4%)	25 (8.2%)
Diarrhoea	0	2 (1.9)	2 (2.0)	4 (2.0)	4 (1.3)
Abdominal pain upper	0	2 (1.9)	1 (1.0)	3 (1.5)	3 (1.0)
Nausea	0	1 (1.0)	2 (2.0)	3 (1.5)	3 (1.0)
Alanine aminotransferase increased	0	0	2 (2.0)	2 (1.0)	2 (0.7)
Liver function test abnormal	0	0	2 (2.0)	2 (1.0)	2 (0.7)

Source: Section 14.3.1, Post-hoc Table 14.3.1.6.1

Abbreviations: AE = adverse events; bid = twice daily; TEAE =treatment-emergent adverse event; tid=3 times daily

Source: Applicant's CSR DIC3-08-05, p.121

Trial DIC3-08-06

A total of 97 (16.1%) subjects discontinued due to a TEAE (Table 31). The table shows the frequency of withdrawals was about equal between treatment groups (10.1% in BID group and 11.6% in the TID group). The most common reason for discontinuation was due to aminotransferase elevation [n= 9 (1.5% in BID group and n=7 (2.3%) on TID group].

Table 31: Subjects With Most Frequent TEAEs Leading to Trial Drug Discontinuation (≥2 Subjects in any Treatment Group) by Preferred Term According to Treatment at Time of Event – Safety Population

Preferred Term	Diclofenac Nanoformulation Capsules Number and Percentage of Subjects (n [%])		
	35 mg bid n=601 n (%)	35 mg tid n=302 n (%)	Combined[b] N=601 n (%)
Any TEAE leading to trial drug discontinuation[a]	61 (10.1)	35 (11.6)	97 (16.1)
Alanine aminotransferase increased	6 (1.0)	4 (1.3)	10 (1.7)
Aspartate aminotransferase increased	3 (0.5)	3 (1.0)	6 (1.0)
Nausea	6 (1.0)	0	6 (1.0)
Abdominal pain	4 (0.7)	1 (0.3)	5 (0.8)
Blood creatinine increased	1 (0.2)	3 (1.0)	5 (0.8)
Liver function test abnormal	4 (0.7)	1 (0.3)	5 (0.8)
Osteoarthritis	3 (0.5)	2 (0.7)	5 (0.8)
Diarrhoea	3 (0.5)	1 (0.3)	4 (0.7)
Dizziness	3 (0.5)	1 (0.3)	4 (0.7)
Abdominal pain upper	2 (0.3)	1 (0.3)	3 (0.5)
Blood pressure increased	1 (0.2)	2 (0.7)	3 (0.5)
Haematuria	2 (0.3)	1 (0.3)	3 (0.5)
Abdominal discomfort	2 (0.3)	0	2 (0.3)
Haematochezia	2 (0.3)	0	2 (0.3)
Hypertension	0	2 (0.7)	2 (0.3)
Insomnia	2 (0.3)	0	2 (0.3)
Myocardial infarction	2 (0.3)	0	2 (0.3)

Source: Section 14.3, Table 14.3.8.1

Source: Applicant's CSR DIC3-08-06, p. 91

A review of the case summaries and analysis provided by the Applicant show that there is no clear trend in discontinuations being related to a dosing group. However, one subject (119-003) met criteria for Hy's Law (i.e., ALT values ≥3 × ULN, AST values ≥3 × ULN, and bilirubin values ≥2 × ULN).

Case 119-003

The subject was a 60 year-old African American female with a medical history significant for osteoarthritis of both knees. She received her first dose of diclofenac 35 mg BID on January 24, 2012 and her dose was increased to 35 mg TID on January 31, 2012. On July 10, 2012 she developed elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood bilirubin increased and moderate blood lactate dehydrogenase increase. Her relevant lab values are shown below in Table 32. Concomitant medications ongoing at the time of the onset of the AEs included the following: multivitamins (plain) and atenolol. Trial drug was discontinued due to the

events and the final dose was given on July 12, 2012. After discontinuation her liver function returned to normal values.

Table 32: Hepatic Function Tests for Subject 119-003

Date (Visit)	Alkaline Phosphatase (42-98 U/L)	ALT (0-33 U/L)	AST (14-34 U/L)	Total Bilirubin (5.13-20.52 µmol/L)
16JAN2012 (Screening)	104[a]	27	25	8.6
21FEB2012 (Week 4)	186[a,b]	58[a]	77[a]	6.8
20MAR2012 (Week 8)	121[a]	27	31	8.6
17APR2012 (Week 12)	126[a]	73[a]	54[a]	10.3
10JUL2012 (Week 24)	236[a,b]	736[a,b]	992[a,b]	112.9[a,b]
16JUL2012 (Week 52/ET)	268[a,b]	947[a,b]	1507[a,b]	241.1[a,b]
23JUL2012 (Unscheduled)	224[a,b]	669[a,b]	1154[a,b]	335.2[a,b]
07AUG2012 (Unscheduled)	162[a,b]	162[a,b]	239[a,b]	177.8[a,b]
28AUG2012 (Unscheduled)	91	25	47[a]	63.3[a,b]

Data source: Appendix 16.2.8, Listing 16.2.14.1.2

Source: Case Narrative for Subject 119-003 in DIC3-08-06

I concluded from this review that the likely cause of the event was related to diclofenac. The product labeling for Cataflam states a higher incidence of elevated ALT and AST values were observed in the open-label study in diclofenac compared to other NSAIDs. Also, elevations in transaminase were seen more frequently in patients with osteoarthritis than those with rheumatoid arthritis. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver failure leading to transplantation or death. Given the information in the already approved reference drug, Cataflam, this information does not require any labeling changes.

7.3.4 Significant Adverse Events

Trial DIC3-08-05

In DIC3-08-05, the majority of events were of mild to moderate intensity. Severe TEAEs were reported for 11 subjects (3.6%): 6 subjects (5.8%) in the diclofenac 35 mg TID group and 2 subjects (2.0%) in the diclofenac 35 mg BID group, compared with 3 subjects (2.9%) in the placebo group. A breakdown of the severe TEAEs is summarized below in Table 33. Due to the small number of severe TEAEs, there is no identifiable trend between groups.

Table 33: Summary of Severe TEAEs by Preferred Term – Safety Population DIC3-08-05

Preferred Term, n (%)	Placebo n=103	Diclofenac Nanoformulation Capsules 35 mg bid n=104	35 mg tid n=98	Combined n=202	Total n=305
Any severe TEAE[a]	3 (2.9)	6 (5.8)	2 (2.0)	8 (4.0)	11 (3.6)
Noncardiac chest pain	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Appendicitis	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Gastroenteritis	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Gastroenteritis (viral)	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Nasopharyngitis	1 (1.0)	0	0	0	1 (0.3)
Back pain	1 (1.0)	0	0	0	1 (0.3)
Muscle spasm	0	0	1 (1.0)	1 (0.5)	1 (0.3)
Hepatic cancer metastatic	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Metastases to lung	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Metastatic neoplasm	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Hemiplegic migraine	1 (1.0)	0	0	0	1 (0.3)
Chronic obstructive pulmonary disease	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Endodontic procedure	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Hypotension	0	1 (1.0)	0	1 (0.5)	1 (0.3)

Source: Section 14.3.1, Table 14.3.1.3 and Post-hoc Table 14.3.1.3.1
Abbreviations: AE = adverse events; bid = twice daily; TEAE =treatment-emergent adverse event; tid=3 times daily.

Source: Applicant's CSR DIC3-08-05, p.120

Trial DIC3-08-06

In trial DIC3-08-06, severe TEAEs were reported for 41 subjects (6.8%) while on either dosing regimen. The most common severe TEAE was osteoarthritis [n=4(0.7%)]. A further breakdown of the severe AE is presented below in Table 34. The data in this table does not show an identifiable difference between the treatment groups with regard to severe TEAEs type or frequency. However, the most common AE, osteoarthritis, was only seen in the BID group. This may suggest the TID dose was more effective over this 52 week study.

Table 34: Severe TEAEs Occurring in More Than 1 Subject Overall by Preferred Term According to Treatment at the Time of the Event – Safety Population

Preferred Term,	Diclofenac Nanoformulation Capsules Number and Percentage of Subjects (n [%])		
	35 mg bid N=601	35 mg tid N=302	Combined[b] N=601
Any severe TEAE[a]	21 (3.5)	21 (7.0)	41 (6.8)
Osteoarthritis	4 (0.7)	0	4 (0.7)
Back pain	2 (0.3)	1 (0.3)	3 (0.5)
Abdominal pain	1 (0.2)	1 (0.3)	2 (0.3)
Chronic obstructive pulmonary disease	2 (0.3)	0	2 (0.3)
Diarrhea	0	2 (0.7)	2 (0.3)
Lumbar spinal stenosis	1 (0.2)	1 (0.3)	2 (0.3)
Myocardial infarction	2 (0.3)	0	2 (0.3)
Sciatica	1 (0.2)	1 (0.3)	2 (0.3)
Tooth abscess	0	2 (0.7)	2 (0.3)
Vomiting	0	2 (0.7)	2 (0.3)

Source: Section 14.3, Table 14.3.4.1

Source: Applicant's CSR for DIC3-08-06, p.89

7.3.5 Submission Specific Primary Safety Concerns

None identified for this application.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The safety population for each trial was defined as all subjects who received at least 1 dose of trial drug. TEAEs were defined as AEs with onset at the time of or following the start of treatment with trial drug, or AEs starting before the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For rollover subjects, AEs starting in the period between trials are also considered TEAEs and are assigned to the regimen at the end of DIC3-08-05.

Overall, for the integrated safety population, serious adverse events (SAEs) and severe TEAEs were uncommon (≤7% of subjects). The most frequent TEAEs were: headache, upper respiratory tract infection (URTI), diarrhea, nausea, and urinary tract infection. Severe or serious cardiovascular, gastrointestinal, or renal TEAEs of the type reported in class labeling for NSAIDs were rare (<0.3% of the integrated safety population) and were observed only in the 52-week trial (DIC3-08-06). The integrated safety population from the two studies showed the TEAEs were similar for the 2 diclofenac groups. A description of the individual trials is below.

Trial DIC3-08-05

In trial DIC3-08-05, 202 subjects received at least 1 dose of diclofenac and 155 subjects reported at least 1 TEAE. A higher proportion of subjects in the diclofenac capsules 35 mg TID group (59 subjects [60.2%]) reported ≥1 TEAE compared with subjects in the diclofenac 35 mg BID (50 subjects [48.1%]) and placebo groups (46 subjects [44.7%]). Gastrointestinal events occurred in a higher proportion of subjects in the diclofenac 35 mg TID (21.4%) and diclofenac 35 mg bid (19.2%) groups compared with placebo (13.6%), suggesting a possibly dose response. Nausea was the most frequently reported AE in the diclofenac combined groups (Table 35). Table 35 also shows diarrhea and headache occurred in a greater percentage in the diclofenac groups than placebo with a trend towards greater frequency in the TID group.

Table 35: Summary of Key TEAEs Occurring in at Least 2.0% of Diclofenac Subjects and at Greater Frequency than Placebo in DIC3-08-05

Preferred Term, n (%)	Placebo n=103	Diclofenac 35 mg bid n=104	Diclofenac 35 mg tid n=98	Combined diclofenac n =202
Subjects with ≥1 TEAE	46 (45)	50 (48)	59 (60)	109(54)
Nausea	2 (2)	5 (5)	9 (9)	14 (7)
Diarrhea	3 (3)	5 (5)	7 (7)	12 (6)
Headache	3 (3)	2 (2)	6 (6)	8 (4)
Abdominal pain upper	1 (1)	3 (3)	4 (4)	6 (3)
Sinusitis	1 (1)	2 (2)	3 (3)	5 (2.5)
Vomiting	1 (1)	2 (2)	3 (3)	5 (2.5)
ALT increase	0	1 (1)	3 (3)	5 (2.5)
Creatinine increase	0	1 (1)	3 (3)	4 (2)
Dyspepsia	1 (1)	1 (1)	3 (3)	4 (2)
Flatulence	0	2 (2)	2 (2)	4 (2)
Hypertension	1 (1)	3 (3)	1 (1)	4 (2)
AST increase	0	0	2 (2)	2 (1)

Source: Adapted from DIC3-08-05 CSR, Table 12-6

Trial DIC3-08-06

Overall, 451 subjects reported a total of 1,551 AEs throughout the trial and AEs were reported by a slightly higher percentage while receiving the TID dosing compared with BID dosing, 61.6% and 56.6% respectively. The most frequent AEs by systems organ class were infections and infestations (205 subjects [34.1%]), GI disorders SOC (166 subjects [27.6%]), and musculoskeletal and connective tissue disorders SOC (124 subjects [20.6%]). The most frequent events overall were upper respiratory tract infection (47 subjects [7.8%]; 53 events), headache (46 subjects [7.7%]; 71 events), and urinary tract infection (44 subjects [7.3%]; 50 events). A review of these AEs did not show a trend in the proportion of subjects reporting at least one TEAE by dosing regimen. No substantial differences were identified that would affect my perception of the adverse event profile.

7.4.2 Laboratory Findings

Trial DIC3-08-05

Clinical laboratory tests[15] were performed at Screening, week 6 and end of treatment. A review of the hematologic parameters showed no significant mean changes at any of the follow-up visits. Several subjects displayed abnormal findings with regard to chemistry findings as discussed in the previous sections. Most notable was a change in ALT from baseline in the diclofenac groups. At Week 6, mean increases from baseline for the diclofenac TID (12.9 U/L) and BID (7.2 U/L) treatment groups were numerically higher than for placebo (0.4 U/L), with evidence of a small dose response for the tid and bid groups. At the Week 12/ET assessment, mean increases from baseline were similarly high in the diclofenac tid (15.9 U/L) group; a mean increase of 4.0 U/L was observed for the diclofenac bid group and a decrease of -1.7 U/L was observed for the placebo group. The mean values may be skewed by several cases of elevated ALT values (e.g. up to 534 U/L). Other lab values, such as creatinine, BUN, and bilirubin, showed a slight increase in the mean change from baseline to week 6 and week 12.

There was a small trend of an increase in the number of subjects with chemistry values of potential clinical concern[16] for the tid group of diclofenac when compared to the bid diclofenac group and placebo (Table 36).

[15] Hematology, chemistry (glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, albumin) and urinalysis
[16] ALT or AST >3 x ULN; Alkaline phosphatase > 1.5 ULN; Bilirubin >2 x ULN; BUN ≥24 mg/dl; LDH >2 x ULN; Glucose (random) mg/dL ≥200; Potassium (mmol/L) ≤3.0 or ≥5.5

Table 36: Summary of Subjects With Chemistry Laboratory Values of Potential Clinical Concern - DIC3-08-05

Analyte (unit)	Placebo n=103 n (%)	Diclofenac Nanoformulation Capsules 35 mg bid n=104 n (%)	Diclofenac Nanoformulation Capsules 35 mg tid n=98 n (%)	Diclofenac Nanoformulation Capsules Combined n=202 n (%)	Total n=305 n (%)
Alkaline Phosphatase (U/L)	**1 (1.0)**	**1 (1.0)**	**1 (1.0)**	**2 (1.0)**	**3 (1.0)**
High (Male)	0	1 (1.0)	0	1 (0.5)	1 (0.3)
High (Female)	1 (1.0)	0	1 (1.0)	1 (0.5)	2 (0.7)
ALT (U/L)	**0**	**0**	**4 (4.1)**	**4 (2.0)**	**4 (1.3)**
High (Male)	0	0	0	0	0
High (Female)	0	0	4 (4.1)	4 (2.0)	4 (1.3)
AST (U/L)	**0**	**1 (1.0)**	**2 (2.1)**	**3 (1.5)**	**3 (1.0)**
High (Male)	0	1 (1.0)	0	1 (0.5)	1 (0.3)
High (Female)	0	0	2 (2.1)	2 (1.0)	2 (0.7)
Creatinine (µmol/L)	**1 (1.0)**	**1 (1.0)**	**1 (1.0)**	**2 (1.0)**	**3 (1.0)**
High (Male)	0	0	1 (1.0)	1 (0.5)	1 (0.3)
High (Female)	1 (1.0)	1 (1.0)	0	1 (0.5)	2 (0.7)
BUN (mmol/L)	**10 (10.1)**	**17 (16.3)**	**32 (33.0)**	**49 (24.4)**	**59 (19.7)**
High	10 (10.1)	17 (16.3)	32 (33.0)	49 (24.4)	59 (19.7)
Glucose, random (mmol/L)	**5 (5.1)**	**4 (3.8)**	**6 (6.2)**	**10 (5.0)**	**15 (5.0)**
High	5 (5.1)	3 (2.9)	6 (6.2)	9 (4.5)	14 (4.7)
Low	0	1 (1.0)	0	1 (0.5)	1 (0.3)
LDH (U/L)	**0**	**1 (1.0)**	**0**	**1 (0.5)**	**1 (0.3)**
High	0	1 (1.0)	0	1 (0.5)	1 (0.3)
Potassium (mmol/L)	**3 (3.0)**	**5 (4.8)**	**5 (5.2)**	**10 (5.0)**	**13 (4.3)**
High	3 (3.0)	5 (4.8)	5 (5.2)	10 (5.0)	13 (4.3)

Source: Section 14.3.4, Post-hoc, Table 14.3.3.3

Source: Applicant's CSR DIC3-08-05 p. 141

Overall, the laboratory findings are consistent with known adverse event profile of diclofenac.

Trial DIC3-08-06

The same clinical laboratory tests performed in DIC3-08-05 were performed at screening and weeks 4, 8, 12, 24, 32, 40, and 48; and at Week 52/ET (whichever occurred first). This trial had no placebo group for comparison. The major challenge in reviewing these data are the lack of control group, an extensive assessment period which provided additional time for confounding factors in a population with possible co-morbid conditions. The hematology assessments did not show significant mean

changes from baseline. Chemistry values showed small changes in values, most notably changes in aminotransferases (Table 37). One subject (119-003) met criteria for Hy's Law (i.e., ALT values ≥3 × ULN, AST values ≥3 × ULN, and bilirubin values ≥2 × ULN) discussed in Section 7.3.3. Table 37 shows the mean ALT and AST changes from baseline peak between 8 and 32 weeks, but return closer to baseline by the end of the trial. A similar trend is seen with creatinine values. Overall, these mean changes are small and consistent with the known adverse event profile of diclofenac.

Table 37: Baseline Chemistry Clinical Laboratory Tests and Changes From Baseline – Safety Population DIC3-08-06

Analyte (Unit)	Diclofenac Nanoformulation Capsules 35 mg Combined Mean (SD)								
	Baseline	CFB to Week 4	CFB to Week 8	CFB to Week 12	CFB to Week 24	CFB to Week 32	CFB to Week 40	CFB to Week 48	CFB to Week 52
AP (U/L)	80.7 (21.67)	-0.6 (10.71)	2.4 (11.45)	2.2 (11.24)	-0.1 (14.69)	0.0 (15.46)	0.0 (12.35)	1.9 (13.91)	1.1 (13.58)
ALT (U/L)	28.3 (14.33)	3.2 (12.58)	6.7 (35.34)	5.7 (24.42)	5.0 (39.80)	4.2 (46.42)	3.1 (15.22)	3.5 (14.50)	2.0 (13.19)
AST (U/L)	24.7 (8.88)	1.5 (9.03)	3.6 (19.66)	2.4 (13.25)	4.5 (45.12)	6.0 (71.98)	2.5 (10.14)	2.2 (8.21)	1.9 (8.23)
Bicarbonate (µmol/L)	27.1 (2.13)	0.6 (2.58)	1.5 (2.42)	1.5 (2.28)	0.7 (2.63)	0.6 (2.34)	0.4 (2.27)	0.4 (2.36)	0.3 (2.25)
Bilirubin (µmol/L)	7.94 (3.862)	-0.17 (2.698)	0.06 (2.639)	0.11 (2.736)	0.34 (5.482)	0.91 (11.556)	-0.01 (2.649)	0.26 (2.499)	0.26 (2.554)
BUN (mmol/L)	5.99 (1.849)	0.42 (1.530)	0.39 (1.547)	0.48 (1.594)	0.51 (1.608)	0.43 (1.577)	0.45 (1.527)	0.59 (1.632)	0.60 (1.652)
Creatinine (µmol/L)	83.1 (17.43)	2.9 (9.94)	5.5 (10.02)	4.5 (10.61)	6.2 (11.98)	6.1 (10.92)	2.3 (10.41)	2.3 (11.18)	0.2 (11.80)
Glucose (mmol/L)	5.76 (1.874)	0.15 (1.445)	0.23 (1.431)	0.13 (1.548)	0.11 (1.761)	0.18 (2.071)	0.00 (1.901)	0.06 (1.621)	-0.14 (2.050)
LDH (U/L)	189 3 (35.71)	3.6 (31.58)	6.4 (34.09)	5.1 (33.21)	10.0 (38.09)	9.2 (40.98)	4.6 (35.31)	6.2 (35.87)	1.5 (32.81)
Potassium (mmol/L)	4.46 (0.444)	0.00 (0.448)	-0.01 (0.489)	-0.04 (0.447)	0.03 (0.463)	0.02 (0.441)	0.00 (0.458)	0.07 (0.479)	0.00 (0.494)
Sodium (mmol/L)	140.8 (2.22)	0.1 (2.29)	-0.1 (2.45)	-0.3 (2.60)	0.1 (2.50)	0.1 (2.22)	0.2 (2.35)	0.5 (2.57)	0.3 (2.72)

Source: Section 14.3, Post-hoc Table 14.3.10.1.2a

Source: Applicant's CSR DIC3-08-06, p. 124

7.4.3 Vital Signs

Trial DIC3-08-05

There were no notable differences in vital sign parameters between the diclofenac groups and the placebo group.

Trial DIC3-08-06

There were no notable differences in vital sign parameters between the diclofenac groups.

7.4.4 Electrocardiograms (ECGs)

Trial DIC3-08-05
Two clinically significant abnormal ECGs were reported: 1 in the placebo group (Anterior T wave inversion NCS-sinus bradycardia) and 1 in the diclofenac BID group (sinus bradycardia-NCS lateral T-wave inversion-CS borderline LVH). Neither finding was considered a TEAE. The ECG findings were largely normal and consistent across treatment groups.

Trial DIC3-08-06
No abnormal clinically significant ECG results from the scheduled assessments were reported during the trial. Subjects 102-001, 102-010, 104-023, 108-020, and 108-020 all had abnormal ECG during their cardiac events (i.e., MI or angina), as discussed above.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No special study or analysis was performed to evaluate dose-dependency for AEs. After reviewing the integrated safety population, no clear dose related events were readily identified due to the relative infrequency of the events.

7.5.2 Time Dependency for Adverse Events

There was no formal analysis performed on time dependency for AEs.

7.5.3 Drug-Demographic Interactions

Age
Zorvolex Capsules 35 mg OA clinical trials did not specifically evaluate safety in elderly subjects. NSAIDs include a warning for greater risk of gastrointestinal events, including risk of ulceration, bleeding, and perforation in patients ≥65 years. Therefore the Applicant provided a breakdown of TEAEs for the integrated population by categorical age. A review of these TEAEs did not reveal significant difference by age when viewed by percentage (Table 38).

Table 38: Most Common TEAEs Occurring in >3% of Subjects in Either Age Subgroup by Preferred Term – Integrated Safety Population

	Age Subgroup		Overall
	<65 Years of Age	≥65 Years of Age	
Preferred Term	Zorvolex Capsules 35 mg Combined[a] N=500 n (%)	Zorvolex Capsules 35 mg Combined[a] N=205 n (%)	Zorvolex Capsules 35 mg Combined[b,c] N=705 n (%)
Any TEAE[d]	365 (73.0)	157 (76.6)	522 (74.0)
Headache	40 (8.0)	12 (5.9)	52 (7.4)
Upper respiratory tract infection	34 (6.8)	17 (8.3)	51 (7.2)
Diarrhoea	32 (6.4)	17 (8.3)	49 (7.0)
Nausea	29 (5.8)	18 (8.8)	47 (6.7)
Urinary tract infection	30 (6.0)	15 (7.3)	45 (6.4)
Nasopharyngitis	26 (5.2)	14 (6.8)	40 (5.7)
Constipation	23 (4.6)	13 (6.3)	36 (5.1)
Sinusitis	24 (4.8)	10 (4.9)	34 (4.8)
Osteoarthritis	22 (4.4)	6 (2.9)	28 (4.0)
Cough	22 (4.4)	4 (2.0)	26 (3.7)
Alanine aminotransferase increased	21 (4.2)	4 (2.0)	25 (3.5)
Back pain	19 (3.8)	4 (2.0)	23 (3.3)
Dyspepsia	17 (3.4)	6 (2.9)	23 (3.3)
Abdominal pain upper	14 (2.8)	8 (3.9)	22 (3.1)
Hypertension	12 (2.4)	9 (4.4)	21 (3.0)
Influenza	16 (3.2)	4 (2.0)	20 (2.8)
Bronchitis	9 (1.8)	9 (4.4)	18 (2.6)
Procedural pain	15 (3.0)	3 (1.5)	18 (2.6)

Source: Applicant's Summary of Clinical Safety p.90

Gender

The combined study population consisted of more females (n=433) than males (n=272). However, a review of TEAEs by gender in the integrated safety population did not reveal any safety concerns related to gender (Table 39). As shown in the table below, headache, diarrhea and nausea were slightly more prevalent in females. Urinary tract infections (UTI) only occurred in females, however that is likely due to baseline increase risk of UTIs in females compared with males.

Table 39: Most Common TEAEs Occurring in >3% of Subjects in Either Gender Subgroup by Preferred Term - Integrated Safety Population

	Gender Subgroup		Overall
	Male	Female	
Preferred Term	Zorvolex Capsules 35 mg Combined[a] N=272 n (%)	Zorvolex Capsules 35 mg Combined[a] N=433 n (%)	Zorvolex Capsules 35 mg Combined[b,c] N=705 n (%)
Any TEAE[d]	184 (67.6)	338 (78.1)	522 (74.0)
Headache	15 (5.5)	37 (8.5)	52 (7.4)
Upper respiratory tract infection	17 (6.3)	34 (7.9)	51 (7.2)
Diarrhoea	13 (4.8)	36 (8.3)	49 (7.0)
Nausea	12 (4.4)	35 (8.1)	47 (6.7)
Urinary tract infection	0	45 (10.4)	45 (6.4)
Nasopharyngitis	10 (3.7)	30 (6.9)	40 (5.7)
Constipation	14 (5.1)	22 (5.1)	36 (5.1)
Sinusitis	8 (2.9)	26 (6.0)	34 (4.8)
Osteoarthritis	7 (2.6)	21 (4.8)	28 (4.0)
Cough	8 (2.9)	18 (4.2)	26 (3.7)
Alanine aminotransferase increased	7 (2.6)	18 (4.2)	25 (3.5)
Back pain	9 (3.3)	14 (3.2)	23 (3.3)
Dyspepsia	10 (3.7)	13 (3.0)	23 (3.3)
Abdominal pain upper	5 (1.8)	17 (3.9)	22 (3.1)
Hypertension	12 (4.4)	9 (2.1)	21 (3.0)
Influenza	7 (2.6)	13 (3.0)	20 (2.8)
Bronchitis	5 (1.8)	13 (3.0)	18 (2.6)
Procedural pain	10 (3.7)	8 (1.8)	18 (2.6)
Contusion	2 (0.7)	15 (3.5)	17 (2.4)
Aspartate aminotransferase increased	3 (1.1)	13 (3.0)	16 (2.3)
Fall	1 (0.4)	15 (3.5)	16 (2.3)

Source: Applicant's Summary of Clinical Safety p.89

The majority of the 705 subjects in the study were White or Caucasian (588 [84%]) or Black or African American (109 [15.5%]). Hispanic or Latino accounted for 44 subjects (6%) of the study group. The analysis is limited to the White and Black subgroups. Analyses of TEAEs by race in the integrated safety population did not reveal any safety concerns related to race. The smaller number of black subjects in this treatment group limits the interpretation of this analysis.

7.6 Additional Safety Evaluations

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no instances of overdose in Zorvolex Capsules 35 mg OA clinical trials. Diclofenac does not have abuse potential especially since side effects at therapeutic doses tend to discourage abuse. No evidence was identified in the literature describing the abuse of prescription preparations containing diclofenac.

7.7 Additional Submissions / Safety Issues

No additional safety information, other than already discussed in Section 7, was submitted for review.

8 Postmarket Experience

Zorvolex (diclofenac) Capsules was approved in October 18, 2013. The first Periodic Adverse Drug Experience Report containing safety information during the period from 10/18/2013 through 1/17/2014 was reviewed. No 15-day reports were submitted during the reporting period. No change in the product's current approved labeling was warranted.

9 Appendices

9.1 Literature Review/References

There were no additional literature submissions.

9.2 Labeling Recommendations

Based on review of the proposed labeling provided in the submission, the following are clinical recommendations. My comments are italicized and, they follow the Applicant's proposed wording as it appears in the referenced section of the proposed label.

Section 2.1.2 Osteoarthritis Pain

(b) (4)

Section 6.1 Clinical Trials Experience

Table-2 is a summary of adverse reactions in the Phase 3 study.

(b) (4)

Section 8.4 Pediatric Use

(b) (4)

This statement was not in the previously approved labeling for Zorvolex and no new data was available that would alter the previous language to support this statement. I recommend to not include this language.

14 Clinical Studies

(b) (4)

9.3 Advisory Committee Meeting

No advisory Committee meeting was held for this product.

Appendix

Clinical Investigator Financial Disclosure
Review Template

Application Number: 204592

Submission Date(s): 10/31/13

Applicant: Iroko

Product: Diclofenac acid capsules (Zorvolex)

Reviewer: Steven Galati

Date of Review: 7/21/14

Covered Clinical Study (Name and/or Number): DIC3-08-05 and DIC3-08-06

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 201		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[17] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", attached with a list of investigators at 40 clinical sites, certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure). I counted a total of 201 investigators at these sites. None of the investigators had financial interests or arrangements to disclose, thus the possibility of bias in the results based on financial interests is unlikely.

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

None of the investigators had financial interests or arrangements to disclose, thus the possibility of bias in the results based on financial interests is unlikely.

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/s/

STEVEN A GALATI
07/23/2014

JOSHUA M LLOYD
07/23/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204592 **Applicant:** Iroko **Stamp Date:** October 31, 2013

Drug Name: Zorvolex **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Refers back to SCS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Integrated summary is located in 2.7.3 Summary of Clinical Efficacy.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) referencing Cataflam (N20142)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	DIC3-08-05: A Phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled, 12-week efficacy and safety trial of Zorvolex Capsules 35 mg in subjects with OA pain of the knee or hip. Indication: Osteoarthritis				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Previous trials, literature and two clinical trials in this current sNDA
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			The Applicant meets the previously discussed safety database requirements when all patients are included in the count (i.e., BID and TID dosing regimens). (b) (4) [redacted] However, the exposure appears acceptable.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Provide narratives and case report forms for all subjects who discontinued due to "withdrew consent" for studies DIC3-08-05 and DIC3-08-06.

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

STEVEN A GALATI
12/23/2013

JOSHUA M LLOYD
12/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

CHEMISTRY REVIEW(S)

NDA 204-592, S-002

DIVISION OF NEW DRUG QUALITY ASSESSMENT III
POST-MARKETING, BRANCH IX
Review of Chemistry, Manufacturing, and Controls

NDA #: 204-592 **DATE REVIEWED:** 7/20/2014

OND: DAAAP

REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	CDER DATE
Efficacy	10/31/2013
Amendment	12/27/2013
Amendment	1/31/2014
Amendment	2/6/2014

NAME & ADDRESS OF APPLICANT:

Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

DRUG PRODUCT NAME:

Proprietary: Zorvolex
Established (2013): Diclofenac

PHARMACOL. CATEGORY/INDICATION: Mild to moderate acute pain and osteoarthritis pain in adults

DOSAGE FORM: Immediate Release Capsule

STRENGTHS: 18 mg and 35 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

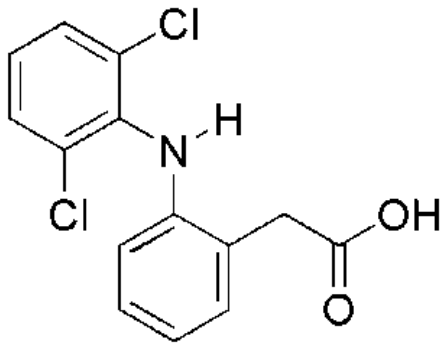
Chemical Name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-

Molecular Formula: $C_{14}H_{11}Cl_2NO_2$

MW: 296.20

CAS #: 15307-86-5

Chemical Structure:



SUPPLEMENT PROVIDES FOR: Treatment of osteoarthritis pain is proposed.

CONCLUSION: Recommend Approval for CMC.

CMC REVIEW:

MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.2 PRESCRIBING INFORMATION:

a. There are no changes pertaining to CMC.

1.12 ENVIRONMENTAL ASSESSMENT:

a. In accordance with 21 CFR 25.31(a) a claim for categorical exclusion is requested.

EVALUATION: Acceptable.

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE:

a. No proposed changes.

3.2.P DRUG PRODUCT:

a. No proposed changes.

EVALUATION: Acceptable.

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/s/

DONALD N KLEIN
07/20/2014
Recommend Approval for CMC; Due 8/31/2014

RAMESH RAGHAVACHARI
07/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	204-592/0014
Drug Name:	Zorvolex (diclofenac acid)
Indication(s):	Treatment of osteoarthritis pain
Applicant:	Iroko Pharmaceuticals, LLC
Date(s):	Received: October 31, 2013
	PDUFA: August 31, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	David Petullo, M.S.
Concurring Reviewers:	Janice Derr, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Medical Officer: Steven Galati, M.D.
	Deputy Division Director: Sharon Hertz, M.D.
Project Manager:	Swati Patwardhan, Ph.D.

Keywords: clinical studies, NDA review, double-blind

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1. EXECUTIVE SUMMARY

Iroko Pharmaceuticals, LCC (Iroko) has submitted a supplemental application (sNDA) evaluating Zorvolex, a novel formulation of diclofenac to support an indication for treatment of pain associated with osteoarthritis (OA). A single study was submitted to support efficacy (Study DIC-08-05) that examined two different dosing regimens of Zorvolex, 35 mg twice daily (BID) and 35 mg three times daily (TID). Based on my review of the data from this study there is evidence that the 35 mg TID dose reduces pain associated with OA as assessed by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain subscale score. My analysis of the primary efficacy endpoint, change in WOMAC pain subscale from baseline to Week 12, indicated that subjects treated with Zorvolex 35 mg TID had on average, a greater reduction in baseline pain at Week 12 when compared to subjects treated with placebo. This was supported by my analyses of secondary endpoints such as the WOMAC composite score and patient global impression of change (PGIC). Though subjects treated with Zorvolex 35 mg BID numerically had larger reductions in baseline pain when compared to placebo subjects, the difference was not statistically significant. Most subjects regardless of treatment used acetaminophen as rescue medication and there was not a significant difference in the percentage of subjects using rescue medication or total amount of rescue medication consumed between any treatment groups.

2. INTRODUCTION

2.1 Overview

Diclofenac is an approved drug in the United States with several indications including relief of the signs and symptoms of OA. Iroko Pharmaceuticals, LLC (Iroko) is developed Zorvolex, a new formulation of diclofenac which the applicant claims improves the dissolution and absorption allowing for a lower dose of diclofenac, hence a better safety profile. This is a 505(b)(2) application and relies on the previous findings of Cataflam for safety and efficacy. Zorvolex was approved on October 18, 2013 for treatment of acute pain.

The clinical development program of Zorvolex for chronic pain was discussed at several meetings under IND 103,880. The protocol for the current study was submitted twice for a Special Protocol Assessment but an agreement was not reached. Statistical reasons for denial mainly focused on how missing data would be handled in the primary analysis. The applicant was also advised to conduct a continuous responder analysis where subjects that discontinued treatment were considered non-responders.

During a telephone conference held on October 26, 2011, there was discussion regarding the flare design utilized in the submitted efficacy study. The applicant was advised that the FDA no longer considers flare design an appropriate design. However, studies currently underway would be allowed to continue and would be acceptable as a study to support efficacy. During a pre-NDA meeting held on May 23, 2013, the company was informed that a single study would be adequate to support filing the sNDA and that the associated statistical analysis plan appeared appropriate. Although it was unclear if the safety database for the TID dose was sufficient. Additionally we expressed concern over how the applicant handled pain scores for subjects that

used rescue medication within 12 hours of a scheduled assessment. If this occurred, any recorded values were considered missing.

2.2 Data Sources

All data was supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

\\Cdsesub1\EVSPROD\NDA204592\0014\m5\datasets

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic data submitted by the applicant was of sufficient quality to allow a thorough review of the data. I was able to derive the primary and secondary endpoints for the submitted study. The statistical analyses of my derived endpoints were in agreement with the applicant's analyses.

The Office of Scientific Investigation did not identify any significant issues during the inspections of sites 101 and 106.

3.2 Evaluation of Efficacy

Study DIC-08-05 was conducted from October 25, 2011 – March 28, 2012 at 40 sites throughout the United States in Arkansas, Arizona, California, Colorado, Florida, Georgia, Kansas, Michigan, Missouri, Nebraska, Nevada, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Texas, and Virginia.

As previously stated, I reviewed the protocol for this study under a special protocol assessment of which an agreement was not reached between FDA and the applicant. Concerns noted were the mixed model repeated measures analysis (MMRM) which assumes that missing data is missing at random. There was also a concern noted with how rescue medication would be handled in the primary analysis. The applicant proposed to use LOCF for the WOMAC pain subscale score for patients who took rescue medication within 12 hours of a scheduled study visit. However, the last observation may not represent the pain level necessitating the use of rescue. Thus, we recommended the applicant assess the pain score just prior to taking rescue medication and use that score for the following study visit.

3.2.1 Study Design and Endpoints

This was a phase 3, randomized, multi-center, double-blind, placebo-controlled trial in subjects with pain due to OA of the hip or knee. Eligible subjects were randomized equally to either placebo, Zorvolex 35 mg BID, or Zorvolex 35 mg TID. Approximately 14 days after the screening visit, subjects were administered the first dose of study drug and continued receiving study drug for 12 weeks. Scheduled site visits were at Weeks 2, 6, 12, and approximately one week after the last dose of study drug. Rescue medication was acetaminophen 500 mg every 4-5 hours as needed not to exceed 3 grams per day.

The pre-specified primary efficacy endpoint was defined as the mean change from baseline in the WOMAC pain subscale score at Week 12 or early termination. The WOMAC pain subscale score consists of five questions regarding pain during walking, using the stairs, in bed, sitting or lying, and standing. Each question is answered on a 100 mm VAS scale with 0 being no pain and 100 the worst possible pain. An overall score was derived by averaging the five scores. Secondary endpoints included PGIC, amount of rescue medication consumed, and the percentage of subjects that achieved at least a 30% and 50% reduction in baseline pain.

The applicant estimated that a sample size of 300 subjects (100/treatment arm) would provide greater than 80% power to detect a clinically relevant difference of 10.75 mm in the primary efficacy endpoint, WOMAC pain subscale. This assumed a standard deviation of 27 mm and used a 2-sided 2-sample *t*-test at the 0.05 significance level.

Patient Disposition, Demographic and Baseline Characteristics

A total of 305 subjects were randomized and treated; 108 placebo, 103 Zorvolex 35 mg BID, and 104 Zorvolex 35 mg TID. Demographics for all randomized and treated patients are shown in Table 1.

Table 1. Demographics for all randomized subjects

Characteristic	placebo	Zorvolex 35mg BID	Zorvolex 35 mg TID
Number of Patients	103	104	98
Age in years			
Mean (SD)	62 (8.4)	61 (8.3)	62 (9.9)
Median	61	60	61
[range]	[45, 82]	[46, 86]	[41, 90]
Gender, n (%)			
Female	71 (69)	64 (62)	68 (69)
Male	32 (31)	40 (38)	30 (31)
Race, n (%)			
Caucasian	82 (80)	79 (76)	83 (85)
Black	20 (19)	23 (22)	14 (14)
Other	1 (1)	2 (2)	1 (1)

Source: Reviewer

This study enrolled mostly Caucasian subjects with slightly more female subjects than males and was consistent amongst treatment groups. The mean age of randomized subjects was approximately 61 years old and was evenly distributed between treatment arms.

There were 57 subjects that did not complete the study, 17 in the placebo arm, 17 in the Zorvolex 35 mg BID arm, and 13 Zorvolex 35 mg TID arm. Reasons for discontinuation are shown in Table 2.

Table 2. Disposition of all randomized subjects

Disposition	placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
Randomized	103	104	98
Completed	86	91	81
discontinued	17	13	17
Reason for Discontinuation			
adverse event	4	9	12
lack of efficacy	6	2	-
withdrawal of consent	2	1	3
protocol violation	2	1	2
lost to follow-up	3	-	-

Source: Reviewer

As expected there were more adverse events in the Zorvolex treatment arms than placebo and more withdrawals due to lack of efficacy in the placebo arm than the Zorvolex arms.

Statistical Methodologies

The analysis dataset defined by the applicant was all randomized subjects who received at least one dose of study drug. The primary efficacy endpoint was defined as the mean change from baseline in the WOMAC pain subscale score at Week 12 or early termination. At least four of the five pain subscale questions had to be answered for the score to be considered valid otherwise the assessment was considered missing in the analysis. If a subject used rescue medication within 12 hours of an efficacy assessment, the score at that visit was considered missing in the analysis. Results were compared between treatment groups using a mixed model repeated measure (MMRM) analysis with no imputation of missing data. To adjust for multiplicity, the TID dose was compared to placebo and if significant, the BID dose was compared to placebo. Secondary endpoints were analyzed according to the type endpoint. Continuous endpoints utilized an analysis of covariance model (ANCOVA) with treatment, site, gender, and the baseline measure in the model. Ordinal endpoints used a Cochran-Mantel-Haenszel (CMH) test for comparisons. There was no testing strategy for the secondary endpoints to account for multiplicity.

To examine the missing at random (MAR) assumption in the primary analysis the applicant conducted several sensitivity analyses. These included graphical assessment of WOMAC pain subscale scores for dropouts, an MMRM analysis were dropouts were penalized, ANCOVA with baseline observation carried forward (BOCF) and last observation carried forward (LOCF), and multiple imputation using a pattern mixture framework.

Overall, the statistical methodologies utilized by the applicant for the analyses of the primary and secondary efficacy outcomes were acceptable. However, their primary analysis assumed an MAR assumption which is not valid in this clinical setting. My concern is that a patient on active drug may have discontinued treatment due to an adverse event. In the MAR setting this patient may receive a treatment benefit in the analysis. I focused on an analysis where the pain score for discontinued subjects returned to baseline. Since all subjects had a baseline score prior to starting treatment, I randomly assigned a baseline score from this distribution of scores. I also considered

BOCF and a modified BOCF/LOCF approach where I used LOCF for placebo subjects and BOCF for subjects on active drug.

Results and Conclusions

When I compared the average change from baseline at Week 12 for the TID and BID doses of Zorvolex to placebo, there was a significant difference noted for the TID dose. There was not a significant difference between placebo and Zorvolex 35 mg BID. A summary of my primary analyses is shown in Table 3. All analyses account for missing pain scores and use of rescue medication.

Table 3. Results from analysis of primary endpoint

Analysis	Imputation	Mean change from baseline pain at Week 12 (stdev)		
		placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
MMRM	none	35.0 (2.9)	41.7(2.8)	46.6 (3.0)*
ANCOVA	BOCF	28.9 (3.2)	36.4 (3.2)	39.3 (3.4)*
ANCOVA	BOCF/LOCF	30.4 (3.2)	38.3 (3.2)	40.1 (3.4)*
ANCOVA	return to BL	28.7 (3.2)	36.4 (3.3)	40.3 (3.5)*

* p-value for comparison to placebo < 0.05

Source: Reviewer

In my analysis, if a subject used rescue medication within 12 hours of scheduled study visit, I randomly assigned a score from the distribution of baseline scores and used this in my analysis. However, there were very few subjects that required rescue medication within 12 hours of a study visit. Hence, I conclude that use of rescue medication did not influence my primary analysis. The number of subjects that used rescue medication within 24 hours of a visit is shown in Table 4.

Table 4. Number of subjects that used of rescue medication within 12 hours of a scheduled study visit

Visit	Number of subjects , n		
	placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
Week 2	0	1	2
Week 6	3	3	1
Week 12	2	1	3
Over-all	5	5	6

Source: Reviewer

Next I examined the amount of missing data at each visit. Note one subject in the Zorvolex BID treatment arm was missing a baseline pain score. This subject should not have been randomized as a baseline score was required for randomization. I considered this subject to be a treatment failure in my analysis. The amount of missing data by visit is shown in Table 5.

Table 5. Missing data by visit

	Number of subjects, n (%)		
Time	Placebo	Zorvolex 35 mg BID	Zorvolex 35 mg TID
baseline	0 (0)	1 (1)	0 (0)
Week 2	9 (9)	4 (4)	3 (3)
Week 6	15 (15)	10 (10)	9 (9)
Week 12	15 (15)	12 (12)	15 (14)

Source: Reviewer

Overall missing data was fairly low and regardless of how I handled it in my analysis, there was a significant treatment effect observed for the TID dose of Zorvolex in the analysis of the primary endpoint. The lack of significance for the BID dose was also consistent across the different analyses, Table 3. Next I examined pain scores by visit with no imputation of missing data. Results are shown in Table 6. Overall, in all treatment groups there was a decrease in the WOMAC pain subscale score at each visit. No formal comparisons were made but numerically the change was greater in the Zorvolex arms than in the placebo arm.

Table 6. Mean WOMAC pain subscale scores by visit

		Visit			
Treatment	statistic	Baseline	Week 2	Week 6	Week 12
Placebo	mean	76.1	52.8	44.1	42.2
	95% CI	[72.9, 79.2]	[47.4, 58.2]	[38.5, 49.6]	[36.4, 48.0]
	n	103	92	87	86
Zorvolex 35 mg BID	mean	74.7	43.1	36.1	32.7
	95% CI	[72.0, 77.4]	[38.2, 48.2]	[30.5, 41.6]	[26.9, 38.4]
	n	103*	100	91	89
Zorvolex 35 mg TID	mean	77.0	38.8	31.7	29.3
	95% CI	[74.2, 79.8]	[33.3, 44.2]	[26.6, 36.8]	[24.1, 34.4]
	n	98	94	86	82

*One subject missing baseline pain score

Source: Reviewer

I also examined the percentage of subjects that achieved at least a 30% and at least a 50% improvement from their baseline pain score at Week12. Subjects that discontinued treatment prior to Week 12 were considered non-responders. In both cases there were more subjects in the Zorvolex treatments arms that achieved at least a 30% improvement and 50% improvement from baseline. For the TID dose of Zorvolex, the difference from placebo was statistically significant, p-value < 0.05. Results are shown in Table 7.

Table 7. Percentage of subjects achieving at least a 30% or 50% improvement

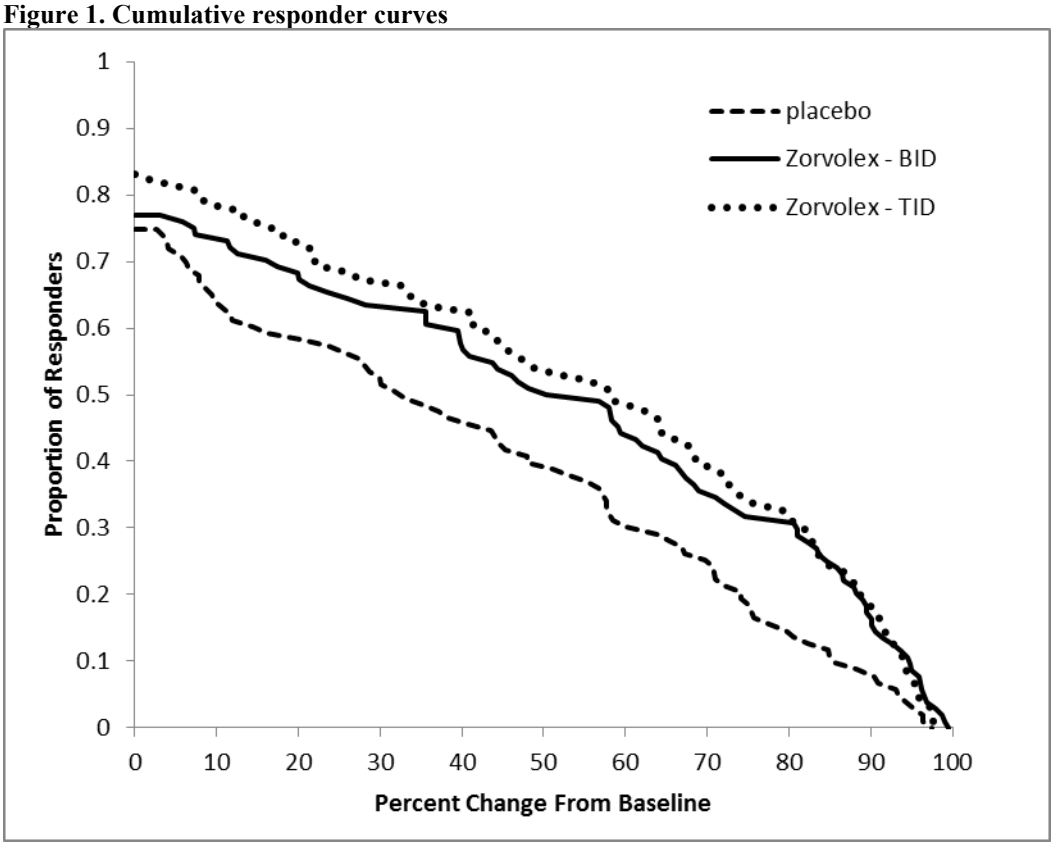
treatment	Percent Improvement from Baseline, % of subjects	
	30%	50%
placebo	52.4	39.8
Zorvolex – BID	63.5	51.0
Zorvolex – TID	67.4*	54.1*

* p-value < 0.05

Source: Reviewer

I also examined cumulative responder curves for each treatment group. Response rates or percent change from baseline were generated from each subject that completed the study. Those that did not complete the study were considered non-responders. There was clear separation between both doses of Zorvolex and placebo at all response levels.

Figure 1. Cumulative responder curves



Source: Reviewer

Secondary endpoints examined were use of rescue medication, the WOMAC composite endpoint, and PGIC. I examined use of recue medication as the percentage of subjects that used rescue medication during the study and the total amount consumed in grams. Results are shown in Table 8. The majority of subjects used rescue medication and there were no significant differences noted between treatment groups.

Table 8. Percentage of subjects that used rescue medication

treatment	n	Used %	Amount LSMEAN (g)
placebo	103	90.2	91.3
Zorvolex – BID	104	94.2	85.6
Zorvolex – TID	98	91.8	75.7

Source: Reveiwer

Next, I examined the change from baseline in the WOMAC composite scores at Week 12. Subjects that did not complete the study were considered as having no change. Results are shown in Table 9. Both doses of Zorvolex, BID and TID, had a larger change from baseline at Week 12 that was significantly different from placebo.

Table 9. WOMAC Composite scores - change from baseline

Treatment	Change from baseline at Week 12		
	LSMEAN	95% CI	Diff from placebo
Placebo	26.1	[20.2, 31.9]	-
Zorvolex – BID	33.8	[27.9, 39.6]	7.7*
Zorvolex – TID	35.6	[29.3, 41.8]	9.5*

*p-value < 0.05

Source: Reviewer

As further evidence of efficacy I examined PGIC scores. I considered scores of 1, 2, or 3 (very much improved, much improved, or minimally improved) a responder. Otherwise a subject was considered a non-responder. Results are shown in Table 10.

Table 10. Comparison of PGIC scores

treatment	% Responders
placebo	56
Zorvolex – BID	73*
Zorvolex – TID	74*

* p-value < 0.01

Source: Reviewer

Both doses of Zorvolex, there were more responders than observed in the placebo arm and the differences were statistically significant.

3.3 Evaluation of Safety

The primary medical officer, Dr. Steven Galati, reviewed the safety data for this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The Applicant examined the primary efficacy endpoint, difference in WOMAC Pain subscale score between baseline and Week 12, for differences due to age or gender. Age was categorized

as less than 65 years old or 65 years or older. To explore any potential differences in the treatment effect by subgroups, I utilized an ANCOVA model with an interaction term for each subgroup. As expected the effect of treatment was consistent for age, gender, and racial subgroups.

As this study was conducted in the United States I did not examine results for differences due to geographic locations. However, I did examine the treatment effect for any differences due to site. As with the other subgroups, the effect of treatment was consistent across sites.

4.2 Other Special/Subgroup Populations

There were no other subgroups of interest that were identified or analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The single study that evaluated Zorvolex in treating chronic pain associated with OA of the hip or knee demonstrated a statistically significant treatment effect in favor of Zorvolex 35 mg TID. My concern over how the applicant considered pain scores for subjects that used rescue medication within 12 hours of a scheduled assessment missing was not an issue as this occurred in less 2% of all efficacy assessments. Missing data was less than 20% and when handled conservatively in my analyses was not a concern. In all cases, the observed treatment effect for Zorvolex 35 mg TID was consistent. The lack of a significant treatment effect in my primary analyses, p-value > 0.05, for Zorvolex 35 mg BID was also consistent.

5.2 Conclusions and Recommendations

In Study DIC3-08-05, the efficacy of Zorvolex 35 mg TID was demonstrated in treating chronic pain associated with OA of the hip or knee as indicated by the significance of the pre-specified primary endpoint and was supported by the significance of various secondary endpoints. There were no concerns regarding the analysis populations, statistical analyses, imputation of missing data, and use of rescue medication that could not be addressed.

5.3 Label Review

Using the label provided in the submission, I have the following comments regarding the information regarding the current study that is included in Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized. It may be beneficial to include the continuous responder curves shown in Figure 1 in the label.

Phase 3 Efficacy Study in Patients with Osteoarthritis Pain

The efficacy of ZORVOLEX in the treatment of osteoarthritis pain was demonstrated in a single multicenter, randomized, double-blind, placebo-controlled, parallel arm study comparing ZORVOLEX 35 mg taken twice a day or three times a day and placebo in patients with clinically and radiologically confirmed osteoarthritis of the knee or hip. The study enrolled 305 patients with a mean age of 62 (range 41 to 90 years). Osteoarthritis pain was measured using the Western Ontario and MacMaster University Osteoarthritis Index Pain Subscale (WOMAC Pain Subscale), a validated questionnaire used to quantify the amount of pain experienced by patients

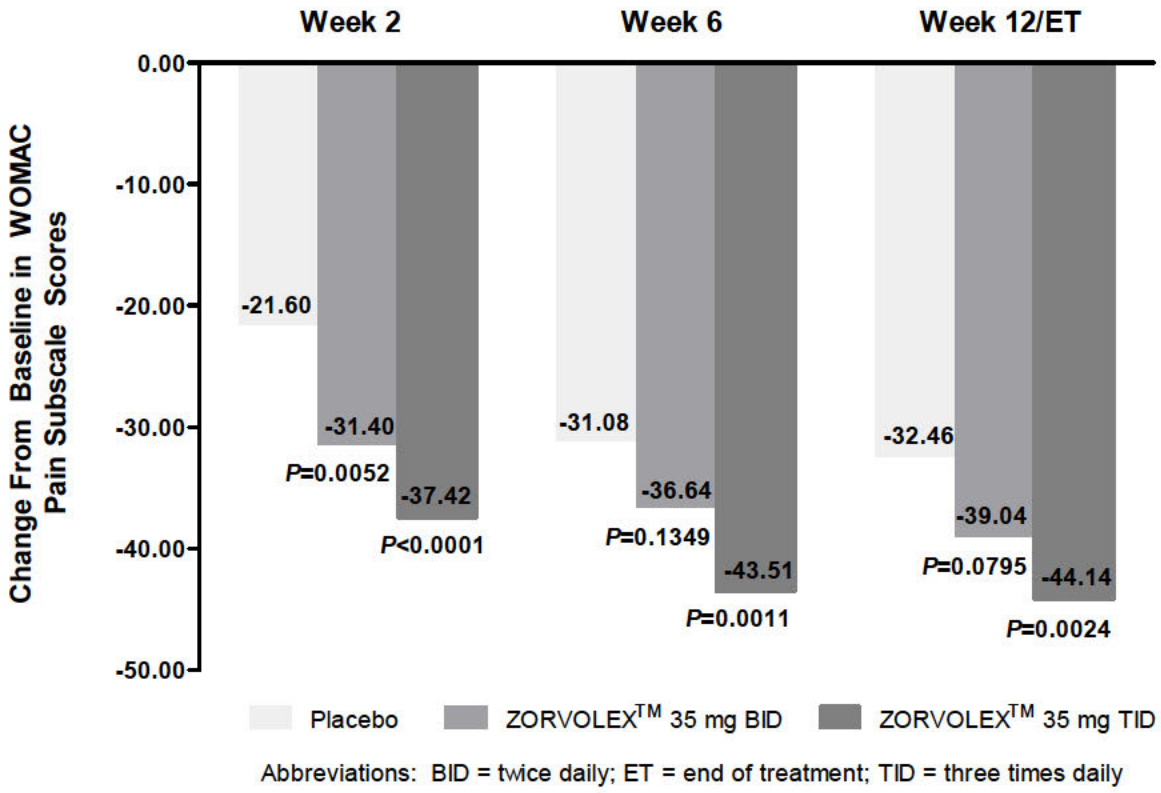
with osteoarthritis. Mean baseline WOMAC Pain Subscale Score across treatment groups was 75 mm using a 0 to 100 mm scale.

The above is consistent with the study report.

The primary efficacy parameter was the change from baseline at 12 weeks in the WOMAC Pain Subscale. Additional secondary efficacy parameters included the change from baseline in WOMAC Pain Subscale at 2 weeks and 6 weeks (Figure 2); and change from baseline in the Total WOMAC Score, including measures of pain, function and stiffness over the 12 week study period and Patient Global Impression of Change (Table 3). The pattern of response in the patient Global Impression of Change assessment was significantly different for the ZORVOLEX treatment groups compared to placebo.

The above information is consistent with the study report and my analyses of the data from Study DIC3-08-05. However, since the applicant's pre-specified analyses of the secondary endpoints were not adjusted for multiplicity, information regarding these analyses should not be included in the label.

Figure 2 ZORVOLEX Study: Change from Baseline WOMAC Pain Subscale at 2, 6 and 12 weeks (Primary Efficacy Parameter)



The primary endpoint in this study was the mean change from baseline in WOMAC pain subscale score at Week 12, not Weeks 2 and 4. Only the Week 12 results should be included in the label.

Table 3 ZORVOLEX Phase 3 Study in Osteoarthritis Pain: Key Secondary Efficacy Parameters

Endpoint	Placebo	ZORVOLEX 35 mg twice daily	ZORVOLEX 35 mg three times daily
Change in WOMAC Score (12 weeks)* Least Squares Mean	-23.22	-30.25	-35.86
P-value versus Placebo	-	0.0363	0.0002
Patient Global Impression of Change (%)			
Very much improved	6	23	26
Much improved	28	28	41
Minimally improved	29	30	21
No change	23	11	9
Minimally worse	4	6	2
Much worse	7	1	1
Very much worse	2	1	0

* Includes pain, function and stiffness assessments.

Patient global impression of change was a secondary endpoint and should not be included in the label.

Comment regarding WOMAC composite score and PGIC, a post-hoc adjustment for multiplicity would have been significant. Therefore, if some clinical benefit is derived from inclusion of these endpoints in the label, I would have no objection.

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/s/

DAVID M PETULLO
07/22/2014

JANICE A DERR
07/23/2014

STATISTICS FILING CHECKLIST FOR NDA 204-592

NDA Number: 204-592 **Applicant:** Iroko **Stamp Date:** October 31, 2013

Drug Name: Zorvolex **NDA Type:** Standard

On **initial** overview of the NDA application for RTF: **Studies DIC3-08-05**

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comment:

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR NDA 204-592

Brief Summary of Pivotal Studies

Study DIC-08-05 was a 12 week, randomized, double-blind, placebo-controlled trial conducted in subjects with osteoarthritis of the knee or hip. Subjects were randomized equally to either placebo, Zorvolex 35 mg twice daily, or Zorvolex 35 mg three times daily. Clinical sites visits were at screening, baseline, and Weeks 2, 6, and 12. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, pain intensity (100 mm VAS), patient global impression of change, and clinical global impression of change were measured at each site visit. Allowed rescue medication was acetaminophen. However, subjects were discouraged from using rescue 24 hours prior to a site visit and were prohibited from using rescue within 12 hours of site a visit. The primary efficacy endpoint was the mean change from baseline in the WOMAC pain subscale at Week 12 or early termination.

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/s/

DAVID M PETULLO
12/23/2013

JANICE A DERR
12/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204592/S-002
NDA 204592/S-004

Name of Drug: Zorvolex (diclofenac) Capsules 18 and 35 mg

Applicant: Iroko Pharmaceuticals

Labeling Reviewed

Submission Date: (S-002) August 21, 2014
(S-004) April 25, 2014

Receipt Date: (S-002) August 21, 2014
(S-004) April 25, 2014

Background and Summary Description: Iroko submitted an efficacy supplement on October 31, 2014, for the use of Zorvolex 35 mg capsules for the treatment of pain of osteoarthritis (OA) in adults to be taken three times a day. A pre-sNDA meeting was held in May 2013, to discuss completeness of the clinical data package for the efficacy supplement. The original application was approved on October 18, 2013, for the treatment of mild to moderate acute pain in adults.

In response to the Division's request for prior approval supplement (PAS), Iroko submitted a PAS (S-004) on April 25, 2014, incorporating safety changes to the medication guide. The labeling review captures changes proposed under S-002 and S-004.

The last approved label for NDA 204592 was under original application approved on October 13, 2014. This was compared to the final label submitted on August 21, 2014, to the pending supplements.

Review

Additions to the last approved labeling are shown in underline text, while deletions are shown in Strikeout.

HIGHLIGHTS OF PRESCRIBING INFORMATION:

11 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin DS®, Tolectin® 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC)

RPM Comment: In addition to the above changes, the minor formatting changes and corrected typographical errors to the package insert and medication guide are acceptable.

Recommendations

The labeling proposed in S-002 and S-004 is recommended for approval.

Concurrence

Swati Patwardhan, RPM **August 21, 2014**

Matthew Sullivan, TL **August 22, 2014**

Josh Lloyd, MO, CDTL **August 22, 2014**

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/s/

SWATI A PATWARDHAN
08/25/2014

MATTHEW W SULLIVAN
08/26/2014

JOSHUA M LLOYD
08/26/2014

EXCLUSIVITY SUMMARY

NDA # 204592 SUPPL # S-002 HFD # 170

Trade Name Zorvolex Capsules

Generic Name diclofenac

Applicant Name Iroko Pharmaceuticals

Approval Date, If Known August 22, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2), SE1 (new Indication)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The supplement added an indication for the treatment of pain of osteoarthritis in adults to be taken three times a day.

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#	020142	Cataflam (diclofenac potassium)
NDA#	021234	Flector (diclofenac epolamine)
NDA#	022202	Zipsor (diclofenac potassium)
NDA#	022165	Cambia (diclofenac potassium)
NDA#	021005	Solaraze (diclofenac sodium)
NDA#	022122	Voltaren (diclofenac sodium)
NDA	19201	Voltaren (diclofenac sodium)
NDA	20254	Voltaren -XR(diclofenac sodium)
NDA#	020947	Pennsaid (diclofenac sodium)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE

SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness

of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Phase 3 clinical trial (DIC3-08-05) and Phase 3 long-term open-label safety study (DIC3-08-06)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously

approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Phase 3 clinical trial (DIC3-08-05)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 113880	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Swati Patwardhan
Title: Regulatory Project Manager, DAAAP
Date: 8/22/2014

Name of Office/Division Director signing form: Sharon Hertz
Title: Deputy Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

SWATI A PATWARDHAN
08/22/2014

SHARON H HERTZ
08/22/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 204592	NDA Supplement #: S- 002	Efficacy Supplement Type SE-
Proprietary Name: Zorvloex Established/Proper Name: diclofenac Dosage Form: Capsules Strengths: 35 mg		
Applicant: **Iroko Pharmaceuticals**		
Date of Receipt: October 31, 2013		
PDUFA Goal Date: August 31, 2014	Action Goal Date (if different): August 29, 2014	
RPM: Swati Patwardhan		
Proposed Indication(s): **treatment of pain of osteoarthritis in adults**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 020142-Cataflam	**FDA's previous finding of safety and efficacy**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Two Phase 1 studies were conducted.

Study DICI-12-07, a pivotal study, was a randomized, single-dose, five-way crossover, relative bioavailability study of Zorvolex™ (diclofenac submicron particle) capsules 18 mg and 35 mg and cataflam® 50 mg tablets, in healthy subjects under fed and fasting conditions, conducted with commercial scale formulation.

The bridging studies were conducted as part of the original application and not this supplement.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Cataflam (diclofenac potassium) Tablets, 50 mg	**020142**	**Y**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The proposed drug product is a reformulation of diclofenac with reduced particle size and is the free acid and not a salt. Cataflam is the potassium diclofenac salt. The proposed drug product is 20% lower in strength compared to the listed drug, Cataflam. The application also provides for a change in dosage from a tablet to a capsule.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity,*

disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

NDA 022122 Voltaren by Novartis
NDA 020947 Pennsaid by Mallinckrodt
NDA 020607 Arthrotec by GD Searle LLC
NDA 020142 Cataflam by Novartic Pharm
And approved generics

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph

III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

SWATI A PATWARDHAN
08/22/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 25, 2014
To:	Bob A. Rappaport, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted Medication Guide (MG)
Drug Name (established name):	ZORVOLEX (diclofenac)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 204592
Supplement Number:	S-002
Applicant:	Iroko Pharmaceuticals, LLC

1 INTRODUCTION

On October 31, 2013, Iroko Pharmaceuticals, LLC submitted for the Agency's review a Prior Approval Efficacy Supplement to their New Drug Application (NDA) 204592/S-002 for ZORVOLEX (diclofenac) capsules. The purpose of this submission is to obtain approval for the proposed indication of treatment of osteoarthritis pain. ZORVOLEX (diclofenac) capsules was originally approved on October 18, 2013 and is indicated for treatment of mild to moderate acute pain in adults.

On December 19, 2013, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for ZORVOLEX (diclofenac) capsules.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed Medication Guide (MG) for ZORVOLEX (diclofenac) capsules.

2 MATERIAL REVIEWED

- Draft ZORVOLEX (diclofenac) capsules MG received on November 1, 2013, resubmitted on April 25, 2014, and received by DMPP on June 10, 2014.
- Draft ZORVOLEX (diclofenac) capsules Prescribing Information (PI) received on October 31, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on July 22, 2014.
- ZORVOLEX (diclofenac) capsules MG approved October 18, 2013.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

/s/

NATHAN P CAULK
07/25/2014

BARBARA A FULLER
07/25/2014

LASHAWN M GRIFFITHS
07/25/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 17, 2014

To: Swati Patwardhan
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204592
OPDP labeling comments for Zorvolex (diclofenac) capsules, for oral use

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In response to DAAAP's December 19, 2013, consult request, OPDP has reviewed the draft Prescribing Information (PI) for Zorvolex (diclofenac) capsules, for oral use that includes changes for S-002. OPDP notes that this efficacy supplement provides an update to Sections 1, 6 and 14 of the PI to include an indication for the treatment of osteoarthritis pain. Therefore, OPDP's comments are limited to the proposed changes to these sections of the PI. There are no proposed changes to the Medication Guide. Therefore, OPDP has not reviewed the Medication Guide at this time.

Comments on the proposed PI and Medication Guide are based on the version sent via email from Swati Patwardhan (RPM) on July 11, 2014. Please note that OPDP's comments on the proposed PI are provided directly on the marked version below.

If you have any questions regarding the package insert, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

24 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EUNICE H CHUNG-DAVIES
07/17/2014

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 14, 2014
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204592/S-002
Product Name and Strength:	Zorvolex (Diclofenac) Capsules 18 mg and 35 mg
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Iroko Pharmaceuticals, LLC
Submission Date:	October 31, 2013
OSE RCM #:	2013-2821
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Iroko Pharmaceuticals submitted this supplement to add a new indication of treatment of osteoarthritis pain. Thus, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) consulted DMEPA to evaluate the proposed changes to the insert labeling from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E
Other	F (N/A)
Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed prescribing information submitted by the Applicant to identify areas of vulnerability that may lead to medication errors. We did not identify any areas of vulnerability in the proposed revisions.

4 CONCLUSION

Our evaluation of the revised prescribing information did not identify any areas of needed improvement. We have no additional comments or edits at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zorvolex that Iroko Pharmaceuticals submitted on October 31, 2013.

Table 2. Relevant Product Information for Zorvolex	
Active Ingredient	Diclofenac
Indication	Proposed: Treatment of osteoarthritis pain Approved: Treatment of mild to moderate acute pain
Route of Administration	Oral
Dosage Form	Capsules
Strengths	18 mg and 35 mg
Dose and Frequency	Proposed indication- 35 mg three times daily. Patients can be titrated from 35 mg (b) (4) three times daily. Approved indication – 18 mg to 35 mg three times daily
How Supplied/Container Closure	Bottles of 30 and 90 capsules
Storage	Room temperature

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 9, 2014 using the criteria in Table 3.

Table 3: FAERS Search Strategy	
Date Range	**October 18, 2013 (Date of FDA Approval) to April 01, 2014**
Drug Names	**Zorvolex** [product name]
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

The search did not yield any cases.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L Drive on April 9, 2014 using the terms, “Zorvolex” to identify reviews previously performed by DMEPA.

C.2 Results

2013-170 Zorvolex (Diclofenac) Label and Labeling Review dated September 12, 2013

We reviewed it to ensure all of our recommendations were considered or implemented. We also reviewed our previous reviews for any issues that may be relevant to this review. Our evaluation found that all of our previous recommendations were implemented.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on April 9, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	April 9, 2014
ISMP Newsletter Search Strategy	Match Exact word or phrase
Search Terms	Zorvolex

E.2 Results

The search did not yield any articles

APPENDIX G. LABELING

G.1 Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Zorvolex prescribing information submitted by Iroko on October 31, 2013.

The Sponsor noted in their submission the container labels, carton labeling, and medication guide were not submitted because there were no proposed changes to them.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

JAMES H SCHLICK
07/14/2014

IRENE Z CHAN
07/14/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204592 BLA#	NDA Supplement #:S- 002 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Zorvolex Established/Proper Name: diclofenac Dosage Form: Capsules Strengths: 18 mg and 35 mg		
Applicant: **Iroko Pharmaceuticals** Agent for Applicant (if applicable): NA		
Date of Application: October 31, 2013 Date of Receipt: October 31, 2013 Date clock started after UN: NA		
PDUFA Goal Date: August 31, 2014	Action Goal Date (if different): August 29, 2014	
Filing Date: December 30, 2013	Date of Filing Meeting: December 18, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): The efficacy supplement proposes for the use of Zorvolex 35 mg capsules for the treatment of pain of osteoarthritis in adults to be taken (b) (4) (b) (4) three times a day.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.*** .		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☒ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 103880

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☒	☐	DARRTS shows 505(b)(1). Per DR, when the filing review will be entered in DARRTS the value will be updated from 505(b)(1) to 505(b)(2)
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.			✓	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	✓	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☒	☐	☐	NP for new clinical investigations exclusivity (3 years) For the same application

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
204592	Zorvolex	**NP**	Oct. 18, 2016

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☐	☒	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	Clinical sites listed, no new manuf. info. No manuf. sites listed
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	From 3542a to be requested from Sponsor
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Electronic submission, No CMC section
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	x			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	x	☐		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	OSI consult is in progress

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐	✓	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 23, 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 18, 2013

BLA/NDA/Supp #: NDA 204592/S-002

PROPRIETARY NAME: Zorvolex

ESTABLISHED/PROPER NAME: diclofenac

DOSAGE FORM/STRENGTH: Capsules, 35 mg

APPLICANT: Iroko Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Addition of indication for treatment of osteoarthritis pain

BACKGROUND:): The efficacy supplement proposes to add treatment to osteoarthritis pain in addition of approved an indication for 35 mg dose taken (b) (4) three times a day. A meeting was held in May 2013 to discuss submission of a supplemental New Drug Application (sNDA) for treatment of osteoarthritis.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Swati Patwardhan	Y
	CPMS/TL:	Matt Sullivan	N
Cross-Discipline Team Leader (CDTL)	Josh Lloyd		Y
Clinical	Reviewer:	Steve Galati	Y
	TL:	Josh Lloyd	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	

	TL:	NA	
Clinical Pharmacology	Reviewer:	Suresh Naraharisetti	N
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Janice Derr	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alex Xu	Y
	TL:	Adam Wasserman	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	NA	
	TL:	NA	
Quality Microbiology *(for sterile products)*	Reviewer:	NA	
	TL:	NA	
CMC Labeling Review	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:	NA	
	TL:	NA	
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:	TBD	
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:	NA	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:	NA	

Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers			
Other attendees	Sharon Hertz, Deputy Director Bob Rappaport		Y

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	This is an efficacy supplement for indication of OA referencing Cataflam NDA 020142. In the original application, data was submitted for a randomized, single-dose, five-way crossover, relative bioavailability study of Zorvolex™ (diclofenac submicron particle) capsules 18 mg and 35 mg and cataflam® 50 mg tablets, in healthy subjects under fed and fasting conditions, conducted with commercial scale formulation
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments	☐ Not Applicable

List comments: None	
CLINICAL **Comments**: Provide narratives and case report forms for all subjects who discontinued due to "withdrew consent" for studies DIC3-08-05 and DIC3-08-06.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☒ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Not submitted to be requested in 74 day letter	 ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☒ Not Applicable ☐ YES ☐ NO

Comments:	
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	

• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Bob Rappaport

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): NA

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Not attached

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

SWATI A PATWARDHAN
01/02/2014

PARINDA JANI
01/02/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 204592/S-002

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Zorvolex (diclofenac) Capsules, 18 and 35 mg

Applicant: Iroko Pharmaceuticals

Receipt Date: October 31, 2013

Goal Date: August 31, 2014

1. Regulatory History and Applicant's Main Proposals

The original application NDA 204592, a 505b2 application, was approved on October 18, 2013, for treatment of acute pain of mild to moderate severity in adults. The efficacy supplement proposes to add for the treatment of osteoarthritis pain in addition of approved indication. A meeting was held in May 2013 to discuss submission of a supplemental New Drug Application (sNDA) for the treatment of osteoarthritis.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiency was identified in the review of this PI. For the deficiency, see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 31, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES**" in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional

Selected Requirements of Prescribing Information

• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES

13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *RMC missing*

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

Selected Requirements of Prescribing Information

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsection 2.1.1 Acute Pain and 2.1.2 Osteoarthritis Pain are bolded*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SWATI A PATWARDHAN
12/31/2013

PARINDA JANI
12/31/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204592/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, August 20, 2014 8:40 PM
To: 'Paul Kirsch'
Subject: RE: NDA 204592/S-002 ZORVOLEX Revised Labeling
Attachments: ZORVOLEX OA Labeling revised Aug 20 2014.doc

Importance: High

Hi Paul,

Attached please find the revised labeling with additional comments. Please send a revised labeling accepting our changes and proposed changes in with track format. Also send a clean copy of the accepted changes (both via email to me).
We request the revised labeling by 2 pm tomorrow.
Please acknowledge the receipt.

Let me know if you have any question.
Thank you
Swati Patwardhan
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

24 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SWATI A PATWARDHAN
08/22/2014

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, July 21, 2014 4:57 PM
To: 'Paul Kirsch'
Subject: RE: NDA 204592/S-002 Zorvolex (diclofenac) capsules-labeling comments
Attachments: zorvolex-current labeling-July 21-2014.doc

Dear Paul,

Attached please find the word version of the labeling with our proposed changes. Please review the proposed FDA revisions, and **email** back to me your response.

You can email me a Word version (in track changes). Please accept any changes with which you concur, and then make any revisions you deem necessary. Please DO **NOT** submit final labeling to the sNDA at this time, but send your response to me only via email. Once we receive your response to these revisions, we will again review the label and then I will get back to you with any further proposed revisions prior to the action date.

Since there were revisions made, we may have missed typos, cross references, etc., and some of the heading formatting might be off. In addition, we have used “20131028” version to make the labeling changes. We should have used “20140122”. Please incorporate changes made to the “20140122” in the current version of labeling, when you send the revised PI to us.

Could you acknowledge the receipt. We request the revised labeling by COB Monday, July 28, 2014.

If you have any questions, do not hesitate to call me.

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

24 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SWATI A PATWARDHAN
07/22/2014

PeRC PREA Subcommittee Meeting Minutes
July 2, 2014

PeRC Members Attending:
Lynne Yao
George Greeley
Daiva Shetty
Wiley Chambers
Susan McCune
Rachel Witten
Shrikant Pagay
Tom Smith
Karen Davis Bruno
Susan McCune
Rosemary Addy
Dianne Murphy
Lily Mulugeta
Rachel Witten
Michelle Roth Cline
Rosemary Addy

PREA

	NDA	*206162*	*Olaparib Full Waiver (Agreed iPSP for this product)*	*Treatment of ovarian cancer*
	NDA	*204592/002*	*Diclofenac Full Waiver*	*Treatment of osteoarthritis pain*

Olaparib Full Waiver

NDA 206162 seeks review of Olaparib for the treatment of ovarian cancer

- The application has a PDUFA goal date of July 25, 2014.
- The application triggers PREA as a new: active ingredient, dosage form, dosing regimen, route of administration and indication.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a full waiver because the disease/condition does not occur in pediatric patients.

Diclofenac Full Waiver

- NDA 204592/002 seeks review of Diclofenac for the treatment of osteoarthritis pain.
- The application has a PDUFA goal date of August 25, 2014.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a full waiver because the disease/condition does not occur in pediatric patients.

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/s/

GEORGE E GREELEY
07/15/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: January 3, 2014

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Steven Galati, MD Medical Officer, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Josh Lloyd, MD, Clinical Team Leader, DAAAP

From: Swati Patwardhan, Regulatory Health Project Manager/DAAAP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 204592/S-002
IND#: 103880
Applicant/ Applicant contact information (to include phone/email):
Iroko Pharmaceuticals
Steven Jensen
Phone: 267-546-3019
email: sjensen@iroko.com
Drug Proprietary Name: Zorvolex
Generic Drug Name: Diclofenac
NME or Original BLA (Yes/No/Not Applicable*): No
Review Priority (Standard or Priority or Not Applicable*): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): treatment of osteoarthritis pain

PDUFA: August 31, 2014
Action Goal Date: August 29, 2014
Inspection Summary Goal Date: July 18, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site Number 101 (b) (4) [redacted] **Principle Investigator:** Alan J. Kivitz, MD, CPI	DIC3-08-05	17	*Indication: Treatment of Osteoarthritis pain* *Primary Endpoint: Mean baseline WOMAC Pain Subscale at 12 weeks compared to baseline*
Site Number 106 (b) (4) [redacted] **Principal Investigator**: Haydn Mikel Thomas, MD	DIC3-08-05	27	*Indication: Treatment of Osteoarthritis pain* *Primary Endpoint: Mean baseline WOMAC Pain Subscale at 12 weeks compared to baseline*

III. Site Selection/Rationale

Iroko has submitted sNDA 204592 for Zorvolex (Diclofenac) capsules for the proposed indication of "treatment of osteoarthritis pain in adults." This product was recently approved for "the treatment of mild to moderate acute pain." The Applicant submitted one pivotal study in support of their application, study DIC3-08-05, and an open-label safety study, DIC3-08-05. The pivotal study was conducted at 40 centers, all within the United States. The clinical sites of the pivotal trial were selected above based primarily on the number of patients enrolled. In addition, site 101 had 5 major protocol violations.

Domestic Inspections:

Reasons for inspections (please check all that apply):

___X_ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Swati Patwardhan* at *301-796-4085 or Steven Galati* at 301-796-7408.

Concurrence: (as needed)

____*Joshua Lloyd*_____ Medical Team Leader
____*Steven A. Galati*___ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for OSI/DGCPC Audit******

- *Notification by sponsor or applicant that they have identified GCP related concerns at site (such notifications may be submitted to IND or NDA/BLA).*
- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Is the concern related to a study conducted under IND?*
- *Were the NDA studies conducted under an IND?*

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/s/

MATTHEW W SULLIVAN
01/23/2014

MATTHEW W SULLIVAN on behalf of SWATI A PATWARDHAN
01/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592/S-002

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Iroko Pharmaceuticals LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Steve Jensen
Sr. VP, Regulatory Affairs & Quality

Dear Mr. Jensen:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 31, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zorvolex (diclofenac) Capsules, 18 mg and 35 mg.

We also refer to your amendment dated December 27, 2013.

This supplemental application proposes to add a new indication, for the use of Zorvolex for the treatment of osteoarthritis pain.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is August 31, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 3, 2014.

During our filing review of your supplemental application, we identified the following potential review issue:

You have not included narratives and case report forms for all subjects who discontinued due to "withdrew consent" for studies DIC3-08-05 and DIC3-08-06 in your submission. Provide this information within 15 days of receipt of this letter.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplemental application.

We also request that you submit the following information:

1. Submit Form 3542a with relevant patent information.
2. Per 21 CFR 25.31(e) either provide a statement of categorical exclusion from preparation of an environmental analysis, with no known extraordinary circumstances or provide an environmental assessment.

During our preliminary review of your submitted labeling, we have identified the following labeling format issue:

In the Table of Content (TOC), all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)]. However, Subsections (b) (4) Acute Pain and (b) (4) Osteoarthritis Pain are (b) (4)

We request that you resubmit labeling that addresses these issues by January 31, 2014. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Bob A Rappaport, MD
Director
Division of Anesthesia, Analgesia,
and Addiction products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor) Swati Patwardhan, RPM, DAAAP, 301-796-4085

REQUEST DATE: 12/19/2013

NDA/BLA NO.:204592

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Zorvolex (diclofenac) 18 mg and 35 mg

PRIORITY CONSIDERATION: Standard

CLASSIFICATION OF DRUG: non-narcotic analgesic

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling) July 21, 2014

SPONSOR: Iroko Pharmaceuticals

PDUFA Date: 8/29/2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\cdsesub1\evsprod\nda204592\0014\

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Iroko has submitted an efficacy supplement for Zorvolex (diclofenac) Capsules for the proposed indication of the treatment of osteoarthritis pain. The original application was recently approved on October 18, 2013, for treatment of acute pain of mild to moderate severity in adults.
Request to evaluate the adequacy of the Med guide

Mid-Cycle Meeting: March 27, 2014
Labeling Meetings: TBD
Wrap-Up Meeting: July 21, 2014
PDUFA: Aug. 31, 2014 (Sun., so effectively Fri Aug. 29)

SIGNATURE OF REQUESTER
Swati Patwardhan

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

SWATI A PATWARDHAN
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Swati Patwardhan, RPM, DAAAP, 301-796-4085

DATE: 12/19/2013	IND NO.	NDA NO.204592/S-002	TYPE OF DOCUMENT	DATE OF DOCUMENT: 10/31/2013

NAME OF DRUG: Zorvolex (Diclofenac) Capsules 18 and 35 mg	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: Non-narcotic Analgesic	DESIRED COMPLETION DATE: Jul 14, 2014

NAME OF FIRM: Iroko Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Iroko has submitted an efficacy supplement for Zorvolex (diclofenac) Capsules for the proposed indication of the treatment of osteoarthritis pain. The original application was approved on Oct. 18, 2013 for indication of treatment of acute pain of mild to moderate severity in adults.
Request to evaluate the adequacy of the carton, and container labels.
EDR link: \\cdsesub1\evsprod\nda204592\0014\

PDUFA Date: Aug. 31, 2014 (effectively Aug. 29, 2014)

SIGNATURE OF REQUESTER: Swati Patwardhan	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

SWATI A PATWARDHAN
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-DDMAC-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) Swati Patwardhan, RPM, DAAAP, 301-796-4085
REQUEST DATE: 12/19/2013	IND NO.	NDA/BLA NO.204592/S-002	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG: Zorvolex (diclofenac) Capsules, 35 mg	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: Non-narcotic Analgesic	DESIRED COMPLETION DATE :July 14, 2013 (Generally 1 week before the wrap-up meeting)
NAME OF FIRM: Iroko Pharmaceuticals		PDUFA Date: October 20, 2013	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\cdsesub1\evsprod\nda204592\0014\

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: Iroko has submitted an efficacy supplement for Zorvolex (diclofenac) Capsules for the proposed indication of the treatment of osteoarthritis pain. The original application was recently approved on October 18, 2013, for treatment of acute pain of mild to moderate severity in adults.

Request to evaluate the adequacy of the PI and Med-guide.

Mid-Cycle Meeting: March 27, 2014
Labeling Meetings: TBD
Wrap-Up Meeting: July 21, 2014
PDUFA: Aug. 31, 2014 (Sun., so effectively Fri Aug. 29)

SIGNATURE OF REQUESTER
Swati Patwardhan

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

SWATI A PATWARDHAN
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204592/S-002

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Iroko Pharmaceuticals LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Steve Jensen
Sr. VP, Regulatory Affairs & Quality

Dear Mr. Jensen:

We have received your Supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 204592

SUPPLEMENT NUMBER: S-002

PRODUCT NAME: Zorvolex (diclofenac) Capsules, 18 mg and 35 mg

DATE OF SUBMISSION: October 31, 2013

DATE OF RECEIPT: October 31, 2013

This supplemental application proposes to add the indication of treatment of osteoarthritis pain.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 30, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SWATI A PATWARDHAN
11/06/2013