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

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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.

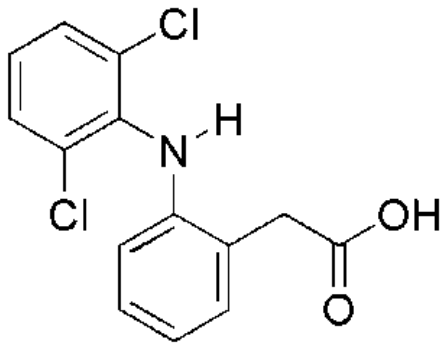
Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen

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

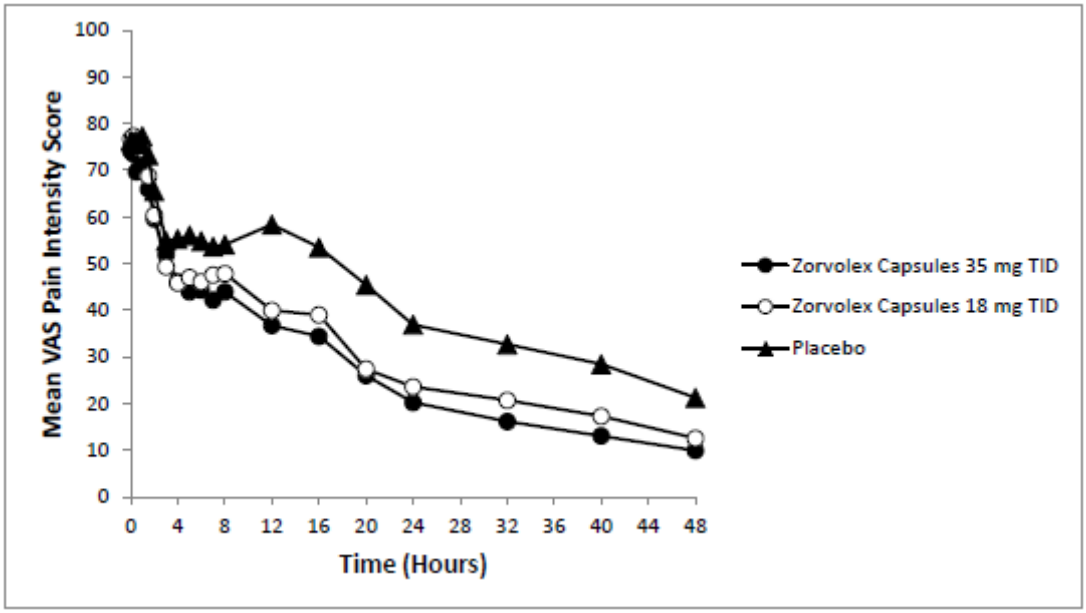
The efficacy of ZORVOLEX in the management of acute pain was demonstrated in a single multicenter, randomized, double-blind, placebo-controlled, parallel arm study comparing ZORVOLEX 18 mg and 35 mg taken three times a day, placebo, and celecoxib in patients with pain following bunionectomy. The study 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



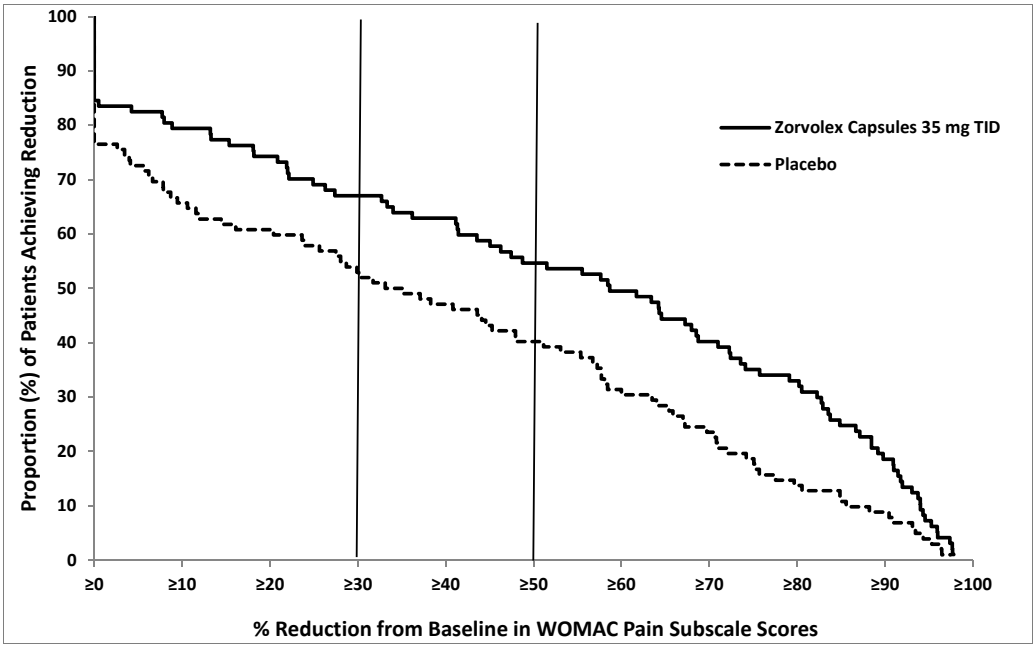
Phase 3 Efficacy Study in Patients with Osteoarthritis Pain

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:
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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:
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Issued: August 2014