

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.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **ZORVOLEX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

RECENT MAJOR CHANGES

Boxed Warning	5/2016
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)	5/2016
Warnings and Precautions, Heart Failure and Edema (5.5)	5/2016

INDICATIONS AND USAGE

ZORVOLEX is a nonsteroidal anti-inflammatory drug indicated for

- management of mild to moderate acute pain (1)
- management of osteoarthritis pain.(1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2)
- The dosage for acute pain is 18 mg or 35 mg orally three times a day. (2)
- The dosage for osteoarthritis pain is 35 mg orally three times a day. (2)

DOSAGE FORMS AND STRENGTHS

ZORVOLEX (diclofenac) capsules: 18 mg and 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)
- In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- **Hypertension:** Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)

- **Heart Failure and Edema:** Avoid use of ZORVOLEX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- **Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ZORVOLEX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- **Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs (5.7)
- **Exacerbation of Asthma Related to Aspirin Sensitivity:** ZORVOLEX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- **Serious Skin Reactions:** Discontinue ZORVOLEX at first appearance of skin rash or other signs of hypersensitivity (5.9)
- **Premature Closure of Fetal Ductus Arteriosus:** Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 2\%$) are 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

- **Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs):** Monitor patients for bleeding who are concomitantly taking ZORVOLEX with drugs that interfere with hemostasis. Concomitant use of ZORVOLEX and analgesic doses of aspirin is not generally recommended (7)
- **ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers:** Concomitant use with ZORVOLEX may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- **ACE Inhibitors and ARBs:** Concomitant use with ZORVOLEX in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- **Diuretics:** NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- **Digoxin:** Concomitant use with ZORVOLEX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of ZORVOLEX in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised 5/2016

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].
- ZORVOLEX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

ZORVOLEX is indicated for:

- Management of mild to moderate acute pain
- Management of osteoarthritis pain

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of ZORVOLEX and other treatment options before deciding to use ZORVOLEX. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

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)*].

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)*]. 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 the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- 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 trials 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, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

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, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials 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. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of ZORVOLEX in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ZORVOLEX is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including diclofenac, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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 occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

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