CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204592Orig1s000

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)**

INDICATIONS AND USAGE

ZORVOLEX is an NSAID indicated for treatment of mild to moderate acute pain in adults. (1)

DOSAGE AND ADMINISTRATION

- The dosage is 18 mg or 35 mg orally three times a day. (2.1)
- Use lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2 1)
- ZORVOLEX capsules are not interchangeable with other formulations of oral diclofenac even if the milligram strength is the same. (2.2)

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. Blood pressure should be monitored closely during treatment with ZORVOLEX. (5.4)
- Fluid retention and edema. ZORVOLEX should be used with caution in patients with fluid retention or heart failure. (5.5)
- Renal papillary necrosis and other renal injury with long-term use. ZORVOLEX should be used 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 clinical trials (incidence ≥2% in ZORVOLEX 18 mg or 35 mg group) include, edema, nausea, headache, dizziness, vomiting, constipation, pruritus, flatulence, pain in extremity, 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 with a dose of ZORVOLEX 18 mg three times a day and if efficacy is not achieved, discontinue use. (2.3, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2013

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

ZORVOLEX is indicated for treatment of mild to moderate acute pain in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

For treatment of mild to moderate acute pain, the dosage is 18 mg or 35 mg three times daily. 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)*].

2.2 Non-Interchangeability with Other Formulations of Diclofenac

ZORVOLEX (diclofenac) capsules do not result in an equivalent systemic exposure to diclofenac as other formulations of oral diclofenac. Other formulations contain a salt of diclofenac, i.e. diclofenac potassium or sodium, while ZORVOLEX contains the free acid. Therefore, do not substitute similar dosing strengths of other diclofenac products for ZORVOLEX.

2.3 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, treatment should be started at the lowest dose. Start treatment with a dose of ZORVOLEX 18 mg three times a day and if efficacy is not achieved, discontinue use.

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 the following:

- 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

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