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

ZUEINO™ (diclofenac sodium) Injection, for intravenous 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)*.**
- **ZUEINO 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)*.**

----------INDICATIONS AND USAGE----------
ZUEINO is a nonsteroidal anti-inflammatory drug indicated for use in adults for the:

- management of mild to moderate pain (1)
- management of moderate to severe pain alone or in combination with opioid analgesics (1)

----------DOSAGE AND ADMINISTRATION----------

- Use for the shortest duration consistent with individual patient treatment goals. (2)
- 37.5 mg administered by intravenous bolus injection over 15 seconds. Treatment may be repeated every 6 hours, not to exceed 150 mg/day. (2)
- Patients must be well hydrated before ZUEINO administration. (2)

----------DOSAGE FORMS AND STRENGTHS----------
ZUEINO (diclofenac sodium) injection, single-dose vial containing 37.5 mg/mL (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)
- Moderate to severe renal insufficiency in the perioperative period and who are at risk for volume depletion. (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 ZUEINO 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 ZUEINO 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: ZUEINO is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue ZUEINO at first appearance of skin rash or other signs of hypersensitivity. (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically. (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including ZUEINO, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>5%) in controlled clinical trials include nausea, constipation, headache, infusion site pain, dizziness, flatulence, vomiting, and insomnia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ADVENTAPHARMA DWC LLC at 1-844-238-3682 (1-844-ADVENTA), 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 ZUEINO with drugs that interfere with hemostasis. Concomitant use of ZUEINO and analgesic doses of aspirin is not generally recommended. (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with ZUEINO may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
- ACE Inhibitors and ARBs: Concomitant use with ZUEINO 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 ZUEINO can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of ZUEINO in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Cardiovascular Thrombotic Events
- 5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
- 5.3 Hepatotoxicity
- 5.4 Hypertension
- 5.5 Heart Failure and Edema
- 5.6 Renal Toxicity and Hyperkalemia
- 5.7 Anaphylactic Reactions
- 5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
- 5.9 Serious Skin Reactions
- 5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- 5.11 Fetal Toxicity
- 5.12 Hematologic Toxicity
- 5.13 Masking of Inflammation and Fever
- 5.14 Laboratory Monitoring

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment
- 8.8 Body Weight

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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)*].**
- **ZUEINO 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

ZUEINO is indicated in adults for the:

- management of mild to moderate pain
- management of moderate to severe pain alone or in combination with opioid analgesics

2 DOSAGE AND ADMINISTRATION

Use for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

ZUEINO is for intravenous administration only.

After observing the response to initial therapy with ZUEINO, the frequency should be adjusted to suit an individual patient's needs. Do not exceed 150 mg total daily dose.

For the treatment of acute pain, the recommended dose of ZUEINO is 37.5 mg administered by intravenous bolus injection over 15 seconds every 6 hours as needed. Maximum daily dose is 150 mg.

To reduce the risk of renal adverse reactions, patients must be well hydrated prior to administration of ZUEINO.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

3 DOSAGE FORMS AND STRENGTHS

ZUEINO (diclofenac sodium) injection: 37.5 mg/mL in a single-dose glass vial. ZUEINO is a clear, colorless to yellowish, aqueous, nonpyrogenic sterile solution.

4 CONTRAINDICATIONS

ZUEINO 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)*]
- Moderate to severe renal insufficiency in the perioperative period and who are at risk for volume depletion [*see Warnings and Precautions (5.6)*]

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 ZUEINO in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ZUEINO 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. ZUEINO is administered by intravenous injection and is intended for acute short-term use. 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.

Strategies to Minimize the GI Risks in NSAID-treated Patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.

- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
  - If a serious GI adverse event is suspected, promptly initiate evaluation and treatment and discontinue ZUEINO until a serious GI adverse event is ruled out.
  - In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity

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

In a large, open-label, controlled trial of 3,700 patients treated with oral diclofenac sodium 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.

In a European retrospective population-based, case-controlled study, 10 cases of diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female sex, doses of 150 mg or more, and duration of use for more than 90 days.

Physicians should measure transaminases at baseline and periodically in patients receiving long-term therapy with diclofenac, 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. ZUEINO is not indicated for long-term treatment. 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.), ZUEINO should be discontinued immediately.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue ZUEINO immediately, and perform a clinical evaluation of the patient.

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

5.4 Hypertension

NSAIDs, including ZUEINO, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events.

Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*]. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of diclofenac may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of ZUEINO in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ZUEINO is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

ZUEINO is not recommended in patients with moderate to severe renal insufficiency and is contraindicated in patients with moderate to severe renal insufficiency in the perioperative period and who are at risk for volume depletion. Acute renal decompensation was observed in 4% out of 68 patients enrolled with renal impairment and treated with diclofenac sodium injection in clinical trials in the perioperative period.

Correct volume status in dehydrated or hypovolemic patients prior to initiating ZUEINO. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of ZUEINO [*see Drug Interactions (7)*]. Avoid the use of ZUEINO in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If ZUEINO is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Diclofenac has been associated with anaphylactic reactions in patients with and without known hypersensitivity to diclofenac and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ZUEINO is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When ZUEINO is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including diclofenac, can cause serious skin adverse reactions such as exfoliative

dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of ZUEINO at the first appearance of skin rash or any other sign of hypersensitivity. ZUEINO is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ZUEINO. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ZUEINO and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including ZUEINO, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ZUEINO, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including ZUEINO, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ZUEINO use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ZUEINO treatment extends beyond 48 hours. Discontinue ZUEINO if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with ZUEINO has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including ZUEINO, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.13 Masking of Inflammation and Fever

The pharmacological activity of ZUEINO in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*]. ZUEINO is not indicated for long-term treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.12)*]

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 practice.

During clinical development, 1,156 patients were exposed to diclofenac sodium injection in multiple-dose, controlled and open-label studies. Diclofenac sodium injection was administered post-surgically every 6 hours for up to 5 days. The incidence rates of adverse reactions listed in the following table are derived from multicenter, controlled clinical studies in post-operative patients comparing diclofenac sodium injection to placebo in patients who may have also received morphine rescue medication.

Table 1: Proportion of Patients Experiencing Common Adverse Reactions in Placebo-Controlled Clinical Studies in Patients with Acute Moderate-to-Severe Postoperative Pain occurring in greater than or equal to 3% in patients treated with Diclofenac Sodium Injection

MedDRA Preferred Term	Placebo* N=126	Diclofenac Sodium Injection* N=187
Any Reaction	104 (83%)	146 (78%)
Nausea	50 (40%)	45 (24%)
Constipation	14 (11%)	25 (13%)
Headache	20 (16%)	19 (10%)
Infusion Site Pain	10 (8%)	19 (10%)
Dizziness	2 (2%)	15 (8%)
Flatulence	20 (16%)	15 (8%)
Vomiting	23 (18%)	12 (6%)
Insomnia	12 (10%)	11 (6%)
Pruritus	10 (8%)	9 (5%)
Hypotension	6 (5%)	9 (5%)
Pyrexia	13 (10%)	8 (4%)
Anemia	9 (7%)	8 (4%)
Infusion Site Extravasation	1 (1%)	6 (3%)

*Intravenous morphine was permitted as rescue medication for pain management.

Adverse reactions of special interest

Based on the analysis of the pooled data from the multi-dose, controlled clinical trials, post-operative patients treated with diclofenac sodium injection had more adverse reactions related to wound healing (7.5%) compared to patients treated with placebo (4%).

Adverse reactions from clinical studies or spontaneous reports for other formulations of diclofenac and other NSAIDs

In patients taking diclofenac or 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: esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice, retching

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 (TEN), erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), urticaria, and fixed drug eruption (FDE)
Special Senses: conjunctivitis, hearing impairment

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with diclofenac.

Table 2: Clinically Significant Drug Interactions with Diclofenac

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Diclofenac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of diclofenac and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of ZUEINO with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].
Aspirin	

Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of ZUEINO and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. ZUEINO is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of ZUEINO and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of ZUEINO and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of ZUEINO with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of ZUEINO and digoxin, monitor serum digoxin levels.

Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of ZUEINO and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of ZUEINO and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of diclofenac and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of ZUEINO and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of diclofenac with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*].
Intervention:	The concomitant use of ZUEINO with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of diclofenac and pemetrexed may increase the risk of pemetrexed- associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of ZUEINO and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

Inhibitors or Inducers of Cytochrome P450 2C9	
Clinical Impact:	Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac.
Intervention:	Use caution when dosing ZUEINO with CYP2C9 inhibitors or inducers, a dosage adjustment may be warranted [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including ZUEINO, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ZUEINO use between about 20 and 30 weeks of gestation, and avoid ZUEINO use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus
Use of NSAIDs, including ZUEINO, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, and rabbits given diclofenac during the period of organogenesis at doses up to approximately 0.7, 0.7, and 1.3 times, respectively, the maximum recommended human dose (MRHD) of ZUEINO despite the presence of maternal and fetal toxicity at these doses. In published studies, administration of clinically relevant doses of diclofenac to pregnant rats produced adverse effects on brain, kidney, and testicular development *(see Data)*.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions
Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including ZUEINO, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment:
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If ZUEINO treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue ZUEINO and follow up according to clinical practice (*see Data*).

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

Data

Human Data
Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data

on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain. Diclofenac has been shown to cross the placental barrier in humans.

Animal Data

Reproductive and developmental studies in animals demonstrated that diclofenac sodium administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (approximately 0.7 times the maximum recommended human dose [MRHD] of ZUEINO, 150 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 0.7 and 1.3 times, respectively, the MRHD based on BSA comparison). In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.1 and 0.2 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal toxicity (peritonitis, mortality) was noted. These 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 and rats.

In published studies, diclofenac administration to pregnant rats prolonged gestation and produced liver toxicity and neuronal loss in offspring (1 mg/kg, IP; 0.07 times the MRHD based on BSA comparison), impaired nephrogenesis in the kidney (3.6 mg/kg, IP; 0.25 times the MRHD based on BSA comparison), and caused adverse effects on the developing testes (6.1 mg/kg, PO; 0.4 times the MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

Data from published literature reports with oral preparations of diclofenac indicate the presence of diclofenac in small amounts in human milk (*see Data)*. There are no data on the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZUEINO and any potential adverse effects on the breastfed infant from the ZUEINO or from the underlying maternal condition.

Data

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).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including ZUEINO, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women *[see Clinical Pharmacology (12.1)]*. Published animal

studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including ZUEINO, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Males
Published studies in adult male rodents report that diclofenac, at clinically relevant doses, can produce adverse effects on male reproductive tissues. The impact of these findings on male fertility is not clear *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ZUEINO have not been established in pediatric patients.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*].

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.

The pharmacokinetics of diclofenac sodium injection are similar in elderly compared to young adults [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

Orally administered diclofenac sodium is extensively metabolized. The pharmacokinetics of diclofenac sodium injection are similar in patients with mild hepatic impairment compared to healthy subjects [*see Clinical Pharmacology (12.3)*]. Dosing adjustments in patients with mild hepatic impairment is not necessary. The pharmacokinetics of ZUEINO were not studied in patients with moderate to severe hepatic impairment and use in this population is not recommended.

8.7 Renal Impairment

Pharmacokinetics of diclofenac sodium injection in patients with mild to moderate renal impairment is similar compared to healthy subjects. However, acute renal decompensation was observed in 4% out of 68 patients enrolled with renal impairment and treated with diclofenac sodium injection in clinical trials in the perioperative period. ZUEINO is not recommended in patients with moderate to severe renal insufficiency and is contraindicated in patients with moderate to severe renal insufficiency in the perioperative period and who are at risk for volume depletion [*see Contraindications (4), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)*].

8.8 Body Weight

Pharmacokinetics of diclofenac following ZUEINO injection appear to be dependent on body weight. The effect of body weight on clinical efficacy and safety of ZUEINO has not been fully studied. Therefore, adjusting dose based on body weight is not recommended [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

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

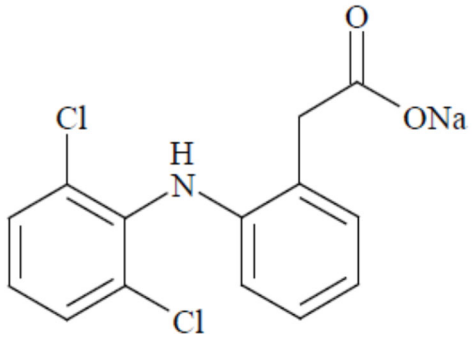
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

11 DESCRIPTION

ZUEINO (diclofenac sodium) injection is a nonsteroidal anti-inflammatory drug for intravenous administration. Each mL of aqueous solution contains 37.5 mg of diclofenac sodium USP (34.8 mg of diclofenac).

Diclofenac sodium USP is a phenylacetic acid derivative that is a white or slightly yellowish, virtually odorless, crystalline powder. The pH of diclofenac sodium USP is 7.0 to 8.5. Diclofenac sodium is freely soluble in methanol; soluble in ethanol; sparingly soluble in water; slightly soluble in acetone; practically insoluble in chloroform and in ether. Its chemical formula and name are: $C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.13] 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid, monosodium salt.



ZUEINO is a clear colorless to yellowish sterile solution filled in a clear glass vial. Each mL of ZUEINO (diclofenac sodium injection) contains the following inactive ingredients: 5 mg monothioglycerol NF, 10 mg polysorbate 80 NF, 80 mg povidone K-12 USP, 2 mg sodium chloride USP, hydrochloric acid NF and/or sodium hydroxide NF used for pH adjustment (8.0 to 9.0), and water for injection USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diclofenac has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of ZUEINO, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

The effect of diclofenac sodium on QTc prolongation was evaluated in a randomized, double-

blind, positive (moxifloxacin 400 mg) - and placebo-controlled crossover study in healthy subjects. A total of 70 subjects was administered diclofenac sodium 37.5 mg and 75 mg. In a study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern.

12.3 Pharmacokinetics

Following intravenous administration of diclofenac sodium to healthy volunteers, plasma concentrations of diclofenac exceed that of immediate-release oral diclofenac for the first 45 minutes reaching a maximum of 4.8-fold 5 minutes after administration.

The pharmacokinetics of diclofenac following intravenous administration of diclofenac sodium injection and oral doses of immediate-release diclofenac are compared in Table 3.

Table 3: Single-dose and Multiple-dose Pharmacokinetics of Diclofenac Sodium Injection and Oral Immediate Release (IR) Diclofenac Potassium

Parameter[1]	Diclofenac Sodium Injection 37.5 mg IV	Oral IR Diclofenac 50 mg PO
Single Dose		
C_{max} (ng/mL)	6,031 ± 1,178	1,246 ±732
T_{max} (h)	0.083	1.5
$AUC_{(inf)}$ (h·ng/mL)	1,859 ± 376	1,562 ± 519
$t_{1/2}$ (h)	1.44 ± 0.27	1.28 ± 0.27
CL (mL/min)	324 ± 63.0	526 ± 179
V_z (L)	40.1 ± 9.77	57.3 ± 20.4
Multiple Dose		
C_{max} (ng/mL)	5,617 ± 1,799	851 ± 462
T_{max} (h)	0.083	1.49
$AUC_{(0-t)}$ (h·ng/mL)	1,839 ± 506	1,350 ± 601
$t_{1/2}$ (h)	2.29 ± 0.63	2.80 ± 0.66
CL (mL/min)	387 ± 394	894 ± 1,392
V_z (L)	83.4 ± 127	242 ± 486

IV=intravenous; PO=oral; [1]CL and V_z are CL/F and V_z/F for oral immediate release diclofenac

Diclofenac sodium administered as an intravenous bolus dose of 37.5 mg every 6 hours for 4 doses to healthy subjects (N=36) showed minimal accumulation with mean values for C_{max} and AUC equivalent between the first and the fourth dose.

Diclofenac sodium exhibits linear pharmacokinetics over intravenous doses ranging from 18.75 to 75 mg and injection times ranging from a bolus (less than 5 seconds) to 60 seconds.

Distribution

Following administration of diclofenac sodium injection, the apparent volume of distribution during the terminal elimination phase (V_z) of diclofenac is 40.1 ± 9.77 L.

Diclofenac is more than 99% bound to human serum proteins, primarily albumin. Serum binding is constant over the concentration range (0.15-105 mcg/mL) achieved with the 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

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.

Plasma concentrations of diclofenac sodium injection decline from peak levels in a biexponential fashion, with a terminal phase half-life of approximately 1.4 hours following intravenous administration.

Total systemic clearance of diclofenac in plasma following administration of diclofenac sodium injection is 324 ± 63 mL/min.

Little or no free unchanged diclofenac is excreted in the urine following administration of diclofenac sodium. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Less than 1% is excreted as unchanged substance.

Specific Populations

Pediatric: The pharmacokinetics of diclofenac sodium injection have not been established in pediatric subjects [*see Use in Specific Populations (8.4)*].

Geriatrics: The effect of aging on the pharmacokinetics of diclofenac sodium injection was studied in 88 subjects from 18 to 86 years old. The terminal half-life for subjects aged 65 to 74 years was

1.4 hours and for subjects greater than or equal to 75 years was 2.1 hours. Clearance of diclofenac following administration of diclofenac sodium injection was not affected by age [*see Use in Specific Populations (8.5)*].

Race: Pharmacokinetics of diclofenac following injection of diclofenac sodium was studied in Caucasian, Black/African and Asian subjects. After taking body weight into account there was no difference in pharmacokinetics of diclofenac with respect to race [*see Pharmacokinetics (12.3)*].

Sex: Systemic exposure of diclofenac was 30% higher in females compared to males following diclofenac sodium injection administration. However, this is possibly due to the effect of body weight on clearance of diclofenac. After taking body weight into account there was no difference in pharmacokinetics of diclofenac with respect to sex [*see Pharmacokinetics (12.3)*].

Hepatic Impairment
The pharmacokinetics of diclofenac sodium injection were evaluated in 8 subjects with mild hepatic impairment (Child-Pugh Classification A, Score of 5 to 6 and a bilirubin of less than or equal to 2.5 mg/dL) compared to matched healthy subjects. The pharmacokinetics of diclofenac following administration of diclofenac sodium injection in mild hepatic impaired subjects were not altered. Pharmacokinetics of diclofenac sodium injection has not been evaluated in moderate or severe hepatic impaired subjects [*see Use in Specific Populations (8.6)*].

Renal Impairment
The pharmacokinetics of diclofenac sodium injection in mild (n = 8), and moderate (n = 5) renal impaired subjects were not significantly altered compared to healthy subjects (n = 7) [*see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)*].

Effect of Body Weight
Pharmacokinetics of diclofenac following diclofenac sodium injection appear to be dependent on body weight. The pharmacokinetics of diclofenac sodium injection were studied in 88 subjects ranging in weight from 53 to 156.2 kg. Clearance of diclofenac in subjects weighing below 95 kg is 282±68 mL/min compared to 356±53 mL/min in subjects above 95 kg body weight (approximately 30% higher clearance). The volume of distribution increased with increased body weight and the proportional increase in clearance resulted in no change in elimination half-life with increased body weight [*see Use in Specific Populations (8.8)*].

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs was reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day

(approximately 0.13 times the maximum recommended human dose [MRHD] of ZUEINO, 150 mg/day, based on mg/m^2 body surface area [BSA] 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 (approximately 0.01 times the MRHD based on BSA comparison) in males and 1 mg/kg/day (approximately 0.04 times the MRHD based on BSA 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 (approximately 0.3 times the MRHD based on BSA comparison) did not affect fertility.

However, published studies report that treatment of adult male rats with diclofenac by the oral route at 10 mg/kg (0.7 times the MRHD based on BSA comparison) for 14 days and at 0.25 mg/kg (0.016 times the MRHD based on BSA comparison) for 30 days produced adverse effects on male reproductive hormones and testes.

14 CLINICAL STUDIES

The effect of diclofenac sodium injection in the short-term treatment of acute pain was evaluated in two double-blind, placebo and active-controlled, multiple-dose clinical trials in patients with postoperative pain. In both trials, intravenous morphine was permitted as rescue medication for pain management.

In a controlled, multiple-dose study of adult patients with postoperative pain who had undergone elective abdominal or pelvic surgery, 245 patients were treated with diclofenac sodium injection, a positive NSAID control (ketorolac tromethamine), or placebo administered every 6 hours starting within 6 hours after surgery and for up to 5 days. The study population consisted of patients with a mean age of 43 years (range 18 to 65 years) and a minimum pain intensity of 50 mm on a 100-mm visual analog scale (VAS) at baseline. The mean baseline pain intensity on the VAS was 68 mm (range 50 to 100 mm). Approximately 63% of subjects in the diclofenac sodium injection 37.5 mg group and 92% of subjects in the placebo group took rescue medication within the first 48 hours of the treatment phase. Efficacy was demonstrated by a reduction in pain intensity as measured by the sum of the pain intensity differences over 0 to 48 hours in patients receiving diclofenac sodium injection as compared to placebo. The average pain intensities over time are depicted for the treatment groups in Figure 1.

In a second controlled, multiple-dose study of adult patients with postoperative pain who had undergone elective orthopedic surgery, 277 patients were treated with diclofenac sodium injection, a positive NSAID control (ketorolac tromethamine), or placebo administered every 6 hours starting within 6 hours postsurgery and for up to 5 days. The study population consisted of patients with a

mean age of 55 years (range 19 to 84 years) and a minimum pain intensity of 50 mm on a 100-mm VAS at baseline. The mean baseline pain intensity on the VAS was 69 mm (range 50 to 100 mm). Approximately 74% of subjects in the diclofenac sodium injection group and 92% of subjects in the placebo group took rescue medication within the first 48 hours of the treatment phase. Efficacy was demonstrated by a reduction in pain intensity as measured by the sum of the pain intensity differences over 0 to 48 hours in patients receiving diclofenac sodium injection as compared to placebo. The average pain intensities over time are depicted for the treatment groups in Figure 2.

Figure 1: Pain Intensity Score Versus Time

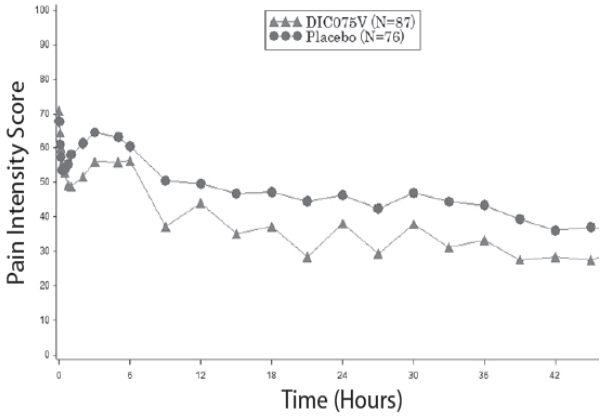
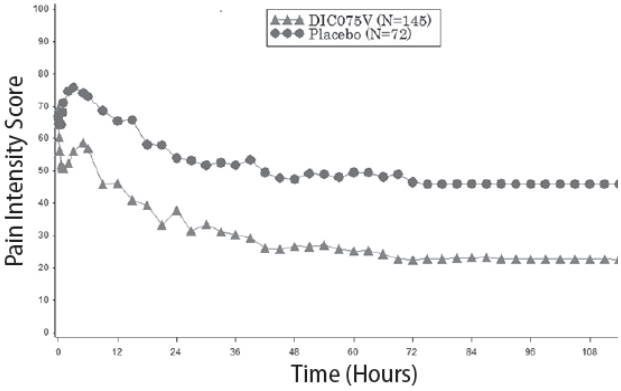


Figure 2: Pain Intensity Score Versus Time



16 HOW SUPPLIED/STORAGE AND HANDLING

ZUEINO (diclofenac sodium) injection, is a clear, colorless to yellowish solution that is supplied as a 1 mL fill in a clear glass vial with a blue tamper-evident top.

NDC No.	Strength	Fill
Carton of 25 (88015-101-02) 1 mL Single-Dose Vial (88015-101-01)	37.5 mg/mL	1 mL Single-Dose Vial

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Do not freeze. Protect from light.

Keep ZUEINO out of reach and sight of children.

Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Inform patients, families, or their caregivers of the following information before initiating therapy with ZUEINO and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity

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

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions, including DRESS

Advise patients to stop ZUEINO immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10)*].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including ZUEINO, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of ZUEINO and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with

ZUEINO is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of ZUEINO with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with ZUEINO until they talk to their healthcare provider [*see Drug Interactions (7)*].

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