

ZORVOLEX[®] is the first FDA-approved low dose NSAID developed using proprietary SoluMatrix Fine Particle Technology[™]. ZORVOLEX is indicated for the management of mild to moderate acute pain and the management of osteoarthritis pain¹.

About ZORVOLEX

ZORVOLEX is the first low dose U.S. Food and Drug Administration (FDA) approved NSAID developed using proprietary SoluMatrix Fine Particle Technology[™]. ZORVOLEX contains diclofenac as submicron particles that are approximately 20 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution. By using this technology, the dose can be lowered without delaying absorption. ZORVOLEX became available in pharmacies across the U.S. in January 2014.

ZORVOLEX Acute Pain Pivotal Phase 3 Data

The FDA approval of ZORVOLEX for the management of acute pain was supported by data from a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel arm study. The study enrolled 428 adult patients with moderate to severe pain following bunionectomy surgery. Participants in the study were randomly assigned to receive ZORVOLEX (18mg or 35mg three times a day), celecoxib (400mg loading dose then 200mg twice daily), or placebo.

The primary efficacy endpoint was the combined differences in pain intensity, calculated as the sum of pain intensity differences by visual analog scale (VASSPID) over 0 to 48 hours (VASSPID-48), following enrollment. The pivotal Phase 3 study showed that patients treated with ZORVOLEX (18mg and 35mg) experienced significant pain relief post surgery compared with placebo (P=0.01 and P<0.001 respectively)².

ZORVOLEX Osteoarthritis Pivotal Phase 3 Data

The FDA approval of ZORVOLEX for the management of osteoarthritis pain was supported by data from a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel arm study. The study enrolled 305 patients with a mean age of 62 (range 41 to 90 years) with clinically and radiologically confirmed osteoarthritis of the knee or hip. Half the patients were between the ages of 61-90. Participants in the study were randomly assigned to receive ZORVOLEX (35mg twice a day or three times a day) or placebo³.

The primary efficacy parameter was the change from baseline at 12 weeks in the WOMAC Pain Subscale. ZORVOLEX (35mg three times a day) significantly improved WOMAC pain subscale scores (-44.1; p=0.0024) compared with placebo (-32.5). 78 percent of patients receiving ZORVOLEX (35mg three times a day) reported at least 30 percent improvement in the WOMAC pain subscale which is considered to be a clinically important improvement. Using the same pain subscale, 63 percent of patients receiving ZORVOLEX (35mg three times a day) reported at least 50 percent improvement. The pattern of response in the Patient Global Impression of Change assessment was significantly different for the ZORVOLEX treatment groups compared to placebo³. The Supplemental New Drug Application (sNDA) also included data from a 12-month open-label safety study that enrolled more than 600 patients¹.

Dosing

ZORVOLEX used for the management of mild to moderate acute pain should be administered in capsule form 18mg or 35mg orally three times a day. ZORVOLEX used for the management of osteoarthritis pain should be administered in capsule form 35mg orally three times a day.

ZORVOLEX should be used at the lowest effective dose for the shortest duration consistent with individual patient treatment goals. ZORVOLEX capsules are not interchangeable with other forms of oral diclofenac, even if the milligram strength is the same.

Safety

Most common adverse reactions in clinical trials (incidence $\geq 2\%$) include: edema, nausea, headache, dizziness, vomiting, constipation, pruritus, diarrhea, flatulence, pain in extremity, abdominal pain, sinusitis, alanine aminotransferase increased, blood creatinine increased, hypertension, and dyspepsia.

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

Important Safety Information

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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.

ZORVOLEX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

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.

ZORVOLEX is contraindicated in patients with: a known hypersensitivity to diclofenac or its inactive ingredients; a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.

ZORVOLEX should be used at the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Elevation of one or more liver tests may occur during therapy with ZORVOLEX. Physicians should measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with ZORVOLEX. ZORVOLEX should be discontinued immediately if abnormal liver tests persist or worsen.

NSAIDs, including ZORVOLEX, can lead to the new onset or worsening of existing hypertension which may contribute to the increased incidence of cardiovascular events. Blood pressure should be monitored closely during treatment with ZORVOLEX. NSAIDs may diminish the antihypertensive activity of thiazides, loop diuretics, ACE inhibitors and angiotensin II antagonists.

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

Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. 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. Treatment with ZORVOLEX in patients with advanced renal disease is not recommended.

Anaphylactoid reactions may occur in patients with the aspirin triad or in patients without prior exposure to ZORVOLEX and should be discontinued immediately if an anaphylactoid reaction occurs.

NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens - Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. ZORVOLEX should be discontinued if rash or other signs of local skin reaction occur.

Starting at 30 weeks gestation, ZORVOLEX and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur.

Concomitant administration of diclofenac and aspirin or anticoagulants is not generally recommended because of the risk of increased GI bleeding that is higher than in users of either drug alone.

Most common adverse reactions in clinical trials (incidence $\geq 2\%$) include: edema, nausea, headache, dizziness, vomiting, constipation, pruritus, diarrhea, flatulence, pain in extremity, abdominal pain, sinusitis, alanine aminotransferase increased, blood creatinine increased, hypertension, and dyspepsia.

ZORVOLEX capsules do not result in an equivalent systemic exposure to diclofenac as other oral formulations. Therefore, do not substitute similar dosing strengths of other diclofenac products for ZORVOLEX.

Please see full Prescribing Information for additional important safety and dosing information.

ZORVOLEX[®] (diclofenac) Capsules

Fact Sheet



¹ ZORVOLEX Prescribing Information 2014, Page 1.

² Gibofsky A., et al. (2013 Sept). Lower Dose Diclofenac Submicron Particle Capsules Provide Early and Sustained Acute Patient Pain Relief in a Phase 3 Study. *Postgraduate Medicine*. 25:130-138.

³ Gibofsky A., et al. (2014 Aug). Efficacy and Safety of Low-Dose Submicron Diclofenac for the Treatment of Osteoarthritis Pain: A 12 Week, Phase 3 Study. *Current Medical Research Opinion*. 1-11.

SoluMatrix Fine Particle Technology[™] is a trademark of iCeutica Inc., and the technology is licensed to Iroko for exclusive use in NSAIDs.

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