



Iroko Pharmaceuticals Announces Acceptance for Filing of ZORVOLEX™ sNDA for the Treatment of Osteoarthritis Pain in Adults

First Lower Dose NSAID Using SoluMatrix Fine Particle Technology™ to be Reviewed by FDA for Treatment of Chronic Pain

PHILADELPHIA, January 15, 2014 — [Iroko Pharmaceuticals, LLC](#), a global specialty pharmaceutical company dedicated to advancing the science of analgesia, announced that the U.S. Food and Drug Administration (FDA) has accepted for review the Supplemental New Drug Application (sNDA) for ZORVOLEX™ (diclofenac), a lower dose nonsteroidal anti-inflammatory drug (NSAID), for the proposed indication of treatment of osteoarthritis pain in adults. ZORVOLEX was approved by FDA in October 2013 for the treatment of mild to moderate acute pain in adults¹.

“FDA’s acceptance of our sNDA filing for ZORVOLEX provides further momentum toward our goal of identifying lower dose treatment options that potentially address the dose-related serious adverse events that accompany traditional NSAIDs,” said John Vavricka, President and CEO of Iroko Pharmaceuticals. “Minimizing the risk of these serious treatment-related adverse events is particularly important in chronic conditions like osteoarthritis where patients may require long-term NSAID treatment to manage their pain.”

ZORVOLEX was developed to address FDA’s public health advisory recommending that NSAIDs be used at the lowest effective dose for the shortest duration consistent with individual patient treatment goals². The risk of serious adverse events, including cardiovascular thrombotic events, myocardial infarction, stroke, gastrointestinal ulcers, gastrointestinal bleeds³ and renal events such as acute renal failure⁴ associated with NSAIDs is higher among patients receiving higher doses⁵.

The sNDA for ZORVOLEX in the treatment of osteoarthritis pain included data from a 12-week, multi-center, randomized, double-blind, parallel-group, placebo-controlled trial that enrolled 305 patients, aged 41-90 years, with osteoarthritis of the hip or knee. Participants were randomized to ZORVOLEX 35mg three times daily or 35mg twice daily, or placebo⁶. Data from this study were presented at the



World Congress on Osteoarthritis in April 2013. The sNDA also included data from a 12-month open-label study that enrolled more than 600 patients.

About ZORVOLEX

ZORVOLEX is the first lower dose 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. ZORVOLEX was developed to align with recommendations from FDA and other professional medical organizations that NSAIDs be used at the lowest effective dose for the shortest possible duration consistent with individual patient treatment goals. For more information, visit www.zorvolex.com.

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

Important Safety Information about ZORVOLEX

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 higher than users of either drug alone.

Most common adverse reactions in clinical trials (incidence $\geq 2\%$) include: edema, nausea, headache, dizziness, vomiting, constipation, pruritus, flatulence, pain in extremity, 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.

About Iroko Pharmaceuticals, LLC

Iroko is a global specialty pharmaceutical company, based in Philadelphia, dedicated to advancing the science of analgesia. The company develops and globally commercializes pharmaceutical products. In addition to the Iroko products that are marketed worldwide, the company has a robust pipeline of investigational lower dose NSAID products being developed using iCeutica Pty Ltd's proprietary SoluMatrix Fine Particle Technology™. For more information, visit www.iroko.com.

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

ZORVOLEX is a trademark of Iroko Pharmaceuticals, LLC.

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¹ ZORVOLEX Prescribing Information

² U.S. Food and Drug Administration. Public Health Advisory - FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

³ Rahme E et. al. (2001 Aug). Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients. Br J Clin Pharmacol. 52(2): 185-192.

⁴ Annual Review of Medicine, Nonsteroidal Antiinflammatory Drugs and Renal Function. Vol. 35: 411-428. DOI: 10.1146/annurev.med.35.020184.002211.

⁵ Risser A. (2009 Dec). NSAID Prescribing Precautions. Am Fam Physician. 80(12):1371-1378.

⁶ Gibofsky A., Hochberg, M., Young, C. (2013 Apr) Phase 3 Study of Lower-dose Diclofenac Submicron Particle Capsules Demonstrates Effective Pain Relief in Patients with Osteoarthritis