MPR

PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to provide you with this PRESCRIBING ALERT about ZORVOLEX™ (diclofenac) capsules, which is indicated for treatment of mild to moderate acute pain in adults and distributed by Iroko Pharmaceuticals, LLC.[1]

ZORVOLEX™ is the first lower-dose NSAID created using SoluMatrix Fine Particle Technology™.[2] By applying this technology, the particle size is reduced to approximately 20 times smaller than its original size which increases the surface area and leads to faster dissolution.[2]

ZORVOLEX™ has a unique pharmacokinetic profile. Both lower doses of ZORVOLEX 18 mg and 35 mg have similar times to peak plasma levels and early (within 1 hour) drug plasma concentrations as the higher dose of diclofenac potassium IR 50 mg.[1,2] If you simply reduce the dose of a traditional NSAID, you would expect a delay in reaching peak drug plasma concentration.[3] This delay is not present with ZORVOLEX™ capsules.

IMPORTANT SAFETY INFORMATION

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.

(Important Safety Information continued on next page)

IMPORTANT SAFETY INFORMATION (*continued*)

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 ≥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 complete Important Safety Information and full Prescribing Information.

More information about ZORVOLEX™ is available in the current edition of *MPR*.

Sincerely,

Asha Gupta, PharmD
Clinical Communications Specialist
MPR Custom Programs

REFERENCES

1. ZORVOLEX™ [prescribing information]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2013. **2.** Data on file, Iroko Pharmaceuticals, LLC. **3.** John VA. The pharmacokinetics and metabolism of diclofenac sodium (Voltarol) in animals and man. *Rheumatol Rehabil*. 1979;(Suppl 2):22-37.

This alert is supported by Iroko Pharmaceuticals, LLC.

Zorvolex™

(diclofenac) capsules

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Company: Iroko Pharmaceuticals, LLC

Pharmacologic class: NSAID (benzeneacetic acid derivative).

Active ingredients: Diclofenac 18 mg, 35 mg; caps; contains gelatin.

Indication: Mild to moderate acute pain in adults.

Pharmacology: ZORVOLEX™ is an NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities. Its mechanism of action is not completely understood but may involve inhibition of COX-1 and COX-2 pathways.

Dosing: >18yrs: 18 mg or 35 mg 3 times daily. Hepatic impairment: initially 18 mg 3 times daily; discontinue if not effective. <18yrs: not established.

Contraindications: 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. Perioperative pain in the setting of CABG surgery.

Adverse Reactions: Edema, nausea, headache, dizziness, vomiting, constipation, pruritus, flatulence, pain in extremity, dyspepsia, rash (discontinue if occurs), GI ulcer/bleed, elevated liver enzymes (discontinue if hepatotoxicity develops), renal papillary necrosis. See labeling for risk of cardiovascular events.

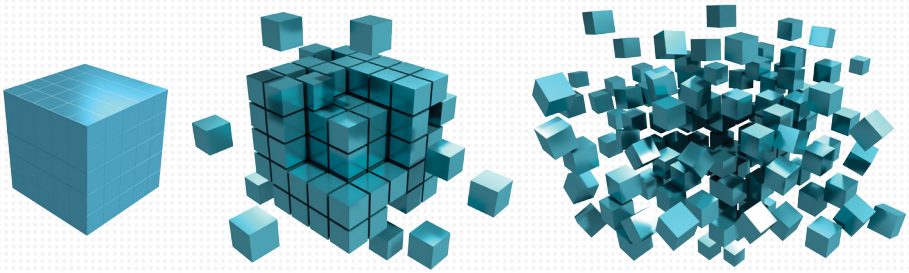
How Supplied: Caps—30, 90

[✓] ZORVOLEX™ (diclofenac) is the first lower-dose NSAID created using SoluMatrix Fine Particle Technology™[1]

- By applying SoluMatrix Fine Particle Technology, the particle size is reduced to approximately 20 times smaller than its original size which increases the surface area and leads to faster dissolution[1]

SOLUMATRIX FINE PARTICLE TECHNOLOGY™ CREATES SUBMICRON PARTICLES

Increased surface area leads to faster dissolutions[1]



Source: Data on file.[1]

- ZORVOLEX™ is available in low doses of 18 mg and 35 mg, which are 20% lower than doses of diclofenac potassium IR (25 mg and 50 mg)[1,2]

Please see complete Important Safety Information and full Prescribing Information.

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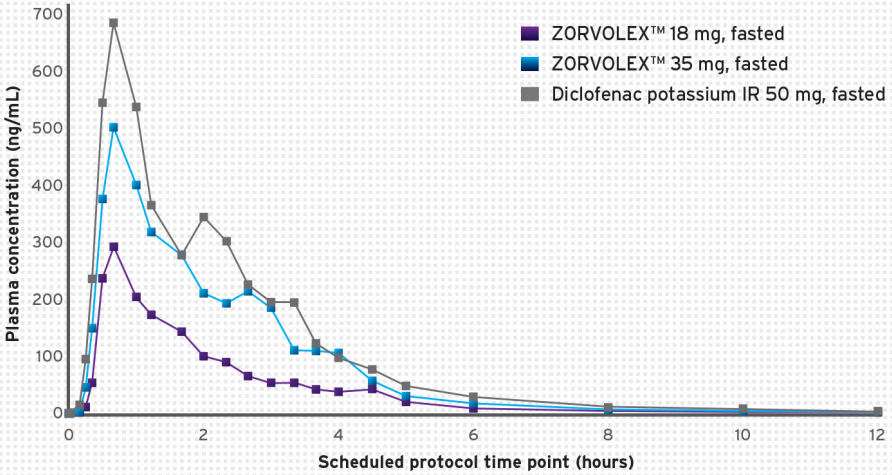
ZORVOLEX™ provides a unique pharmacokinetic profile*

ZORVOLEX™ 18 MG AND 35 MG ACHIEVE COMPARABLE TIMES TO PEAK PLASMA LEVELS AS DICLOFENAC POTASSIUM IR 50 MG†

Diclofenac plasma concentrations over first 12 hours (mg/mL)[1]



†Based on phase 1 study in healthy subjects.[1]

Source: Data on file.[1]

ZORVOLEX™ PROVIDES LOWER OVERALL SYSTEMIC DRUG EXPOSURE†

ZORVOLEX™ 35 mg[1,2]

23% lower overall systemic exposure vs diclofenac potassium IR

- ZORVOLEX™ 35 mg (LS mean=990)
- Diclofenac potassium IR 50 mg (LS mean=1288)

ZORVOLEX™ 18 mg[1,‡]

62% lower overall systemic exposure vs diclofenac potassium IR

- ZORVOLEX™ 18 mg (LS mean=487)
- Diclofenac potassium IR 50 mg (LS mean=1288)

Abbreviation: LS=least-squares.

†Based on phase 1 study in healthy subjects.[1]

‡Although the 18 mg dose was not directly compared with diclofenac potassium IR 50 mg, based on dose proportional kinetics for ZORVOLEX™ the overall systemic exposure is estimated to be 62% lower.[1]

Sources: Data on file[1]; ZORVOLEX [prescribing information].[2]

***THE CLINICAL RELEVANCE OF THE DIFFERENCES IN PHARMACOKINETIC MEASUREMENTS IS UNKNOWN.**

Please see complete Important Safety Information and full Prescribing Information.

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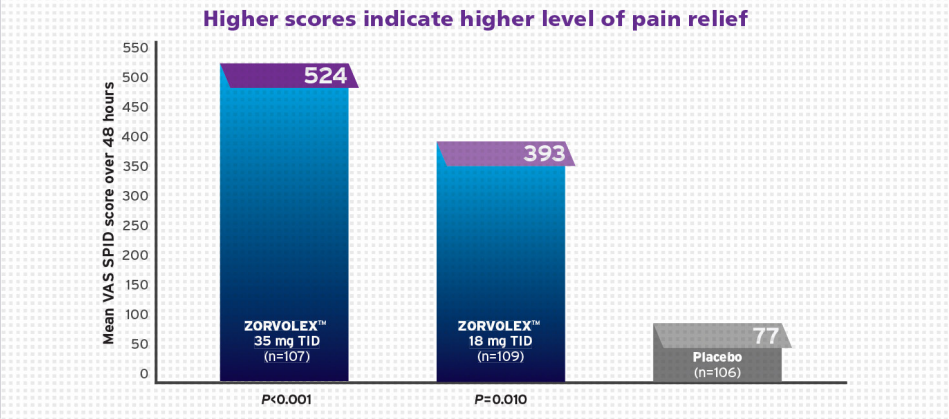
ZORVOLEX™ (diclofenac) provides effective pain relief at low doses: 18 mg or 35 mg TID[1,2]

- Efficacy was demonstrated in a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study comparing ZORVOLEX™ 18 mg and 35 mg, placebo, and celecoxib in 428 patients with pain following bunionectomy[2]

MEAN VISUAL ANALOG SCALE SUM OF PAIN INTENSITY DIFFERENCE OVER 48 HOURS



VAS SPID = visual analog scale sum of pain intensity difference (the sum of pain measurement differences from baseline at all measurement points; higher VAS SPID score indicates higher level of pain relief).

The primary efficacy end point was the combined differences in pain intensity (calculated as the sum of pain intensity differences by visual analog scale over 48 hours following enrollment).[1]

Source: Data on file.[1]

In a postoperative clinical trial, adverse reactions occurred in ≥2% of ZORVOLEX™ (diclofenac) patients and more frequently than with placebo[1,2]

SUMMARY OF ADVERSE REACTIONS

Any treatment-emergent adverse event	ZORVOLEX™ 18 mg and 35 mg TID (n=216)	Placebo (n=106)
Postprocedural edema	33%	32%
Constipation	8%	4%
Pruritus	7%	6%
Flatulence	3%	2%
Pain in extremity	3%	1%
Dyspepsia	2%	1%
Abdominal pain	2%	1%
Procedural pain	2%	0%

Sources: Data on file[1]; ZORVOLEX [prescribing information].[2]

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REFERENCES

1. Data on file, Iroko Pharmaceuticals, LLC. **2.** ZORVOLEX™ [prescribing information]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2013.

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