Pain: *A Public Health Challenge*

Despite advances in understanding and treatment, pain remains a major public health challenge[1] that exacts a significant personal and economic toll on Americans.[1]

- Pain accounts for an estimated 70 million physician visits every year[2]
- Each year, an estimated 20 percent of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more[3]
- Pain costs the U.S. approximately $560-$635 billion annually, or about $2,000 for every American, which is an estimate that combines the incremental cost of health care and the cost of lost productivity attributable to pain[1]
- Approximately one half of U.S. adults report pain or discomfort that persists for longer than three months, and an even greater number are likely to have acute pain at any one time[4]
- More than 76 million people in the U.S. live with chronic pain, and almost half of them receive no treatment[5]
- Osteoarthritis, the most common form of arthritis, affects approximately 27 million U.S. adults each year[6]
- Addressing the safe and effective treatment of pain has been identified as a key objective by The Department of Health and Human Services' (HSS) Healthy People 2020, which provides science-based, 10-year national objectives for improving the health of Americans. Specific goals outlined include:
    - Reducing serious complications from the use of pain medicines
    - Reducing deaths from the use of pain medicines[7]

NSAIDS for Managing Pain

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications for treating pain and inflammation.[8] In the U.S. approximately 123 million NSAID prescriptions were filled in the last year alone.[9]

NSAIDs work largely by inhibiting cyclooxygenase -1 and 2, which are enzymes that control the production of prostaglandins,[10] a family of naturally occurring molecules associated with pain and inflammation.[10] Though effective, NSAIDs have been associated with significant safety concerns, including cardiovascular thrombotic events, myocardial infarction, stroke, gastrointestinal ulcers, gastrointestinal bleeds, and renal events such as acute renal failure. The risk of these serious adverse events is higher among patients receiving higher doses.[11,12,13]

The U.S. Food and Drug Administration (FDA) and many professional medical organizations recommend that NSAIDs be administered at the lowest effective dose for the shortest duration.[14-19] In fact, as recently as July 2015, the FDA announced they would strengthen the existing prescription and over-the-counter labeling for non-aspirin NSAIDs specifically regarding the increased risk of cardiovascular thrombotic events such as myocardial infarction and stroke.[20]

Iroko: *Innovators in Analgesia*

To align with FDA recommendations, Iroko is utilizing SoluMatrix Fine Particle Technology™ to develop low dose formulations of several of the most commonly prescribed NSAIDs. Iroko's portfolio currently includes: ZORVOLEX® (diclofenac) capsules for the management of mild to moderate acute pain and osteoarthritis pain,[21] TIVORBEX® (indomethacin) capsules for the treatment of mild to moderate acute pain in adults[22] and now VIVLODEX™ (meloxicam) capsules for the management of osteoarthritis pain.[23]

Our product pipeline consists of several additional low dose NSAIDs created using proprietary SoluMatrix Fine Particle Technology™ in various stages of nonclinical and clinical development.

IROKO® PHARMACEUTICALS, LLC

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

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 that is higher than in users of either drug alone.

Most common adverse reactions in clinical trials (incidence 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.
For more information, visit www.zorvolex.com

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

Important Safety Information about TIVORBEX

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.

TIVORBEX 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.

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

TIVORBEX 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 NSAIDs, including TIVORBEX. Physicians should measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with TIVORBEX. TIVORBEX should be discontinued immediately if abnormal liver tests persist or worsen.

NSAIDs, including TIVORBEX, 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 TIVORBEX.

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. TIVORBEX 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.

TIVORBEX 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 TIVORBEX in patients with advanced renal disease is not recommended.

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

Indomethacin may aggravate depression, and other psychiatric disturbances, epilepsy, or parkinsonism, and should be used with caution in patients with these conditions. Indomethacin may cause drowsiness; therefore patients should be cautioned about engaging in activities requiring mental alertness and motor coordination. Discontinue TIVORBEX if severe central nervous system (CNS) adverse reactions develop.

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

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

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

Most common adverse reactions in clinical trials (incidence ≥2%) include: nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, constipation, pruritus, diarrhea, dyspepsia, post procedural swelling, presyncope, rash, upper abdominal pain, somnolence, generalized pruritus, hyperhidrosis, decreased appetite, hot flush, and syncope.

VIVLODEX is indicated for the management of osteoarthritis pain.

Important Safety Information about VIVLODEX

Cardiovascular Thrombotic Events
Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular (CV) 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.

VIVLODEX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

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.

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

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

Elevation of one or more liver tests may occur during therapy with VIVLODEX. Rare, sometimes fatal, cases of severe hepatic injury have been reported. VIVLODEX should be discontinued immediately if clinical signs and symptoms of liver disease develop.

NSAIDs, including VIVLODEX, can lead to the new onset or worsening of existing hypertension, which may contribute to the increased incidence of CV events. Blood pressure should be monitored during treatment with VIVLODEX. NSAIDs may diminish the antihypertensive activity of loop and thiazide diuretics, ACE inhibitors, angiotensin receptor blockers, or beta-blockers.

NSAID use has been associated with an increase in the risk of MI, hospitalizations due to heart failure, and death. Also, fluid retention and edema have been observed in patients taking NSAIDs. Avoid the use of VIVLODEX in patients with severe heart failure.

Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. VIVLODEX 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, dehydration, hypovolemia, and those taking diuretics and ACE inhibitors. Avoid the use of VIVLODEX in patients with advanced renal disease. Increases in serum potassium levels, including hyperkalemia, have been reported with NSAID use.

Anaphylactic reactions may occur in patients with the aspirin triad or in patients without prior exposure to VIVLODEX and should be discontinued immediately if an anaphylactic 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. VIVLODEX should be discontinued if rash or other signs of local skin reaction occur.

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

Concomitant administration of anticoagulants, antiplatelet agents (e.g., aspirin), SSRIs, SNRIs, salicylates, or other NSAIDs with VIVLODEX may increase the risk of bleeding.

The anti-inflammatory and anti-pyretic activity of VIVLODEX may mask the signs of infection.

Since serious GI, hepatic, and renal events have been reported with NSAID use, consider monitoring CBC and chemistry profile in patients on long-term NSAID therapy.

Most common adverse reactions in clinical trials (incidence ≥2%) include: diarrhea, nausea, and abdominal discomfort.

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

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. Iroko is at the forefront of the development of SoluMatrix® NSAIDs - new low dose drug products based on existing NSAIDs - using iCeutica Inc.'s proprietary SoluMatrix Fine Particle Technology™ exclusively licensed to Iroko for NSAIDs. ZORVOLEX is the first SoluMatrix® NSAID and is available in pharmacies; the second SoluMatrix® NSAID, TIVORBEX™ was approved by the FDA in February 2014 and is also available by prescription in the U.S. The third SoluMatrix® NSAID, VIVLODEX is now approved by the FDA.
For more information, visit **www.iroko.com.**

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

SoluMatrix® is a registered trademark of iCeutica Pty Ltd and is licensed to Iroko.

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