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[2].

- Pain accounts for an estimated 70 million physician visits every year[3]
- 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[4]
- Pain results in more than 50 million lost workdays every year[5]
- Pain costs the U.S. at least $560-$635 billion annually, or about $2,000 for every American[6]
- 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[7]
- More than 76 million people in the U.S. live with chronic pain, and almost half of them receive no treatment[8]
- Osteoarthritis, the most prevalent pain condition in the U.S., affects approximately 27 million U.S. adults each year[9]
- Increasing 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 injuries from the use of pain medicines
    - Reducing deaths from the use of pain medicines[10]

NSAIDS for Managing Pain

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications for treating pain and inflammation[11]. In the U.S. alone, approximately 115 million NSAIDs are prescribed each year[12].

NSAIDs work largely by inhibiting cyclooxygenase, an enzyme that controls the production of prostaglandins[13], which are a family of naturally occurring molecules associated with pain and inflammation[14]. Though effective, NSAIDs have been associated with significant safety concerns, including cardiovascular thrombotic events, myocardial infarction, stroke[15], gastrointestinal ulcers, gastrointestinal bleeds[16], and renal events such as acute renal failure[17]. The risk of these serious adverse events is higher among patients receiving higher doses[18].

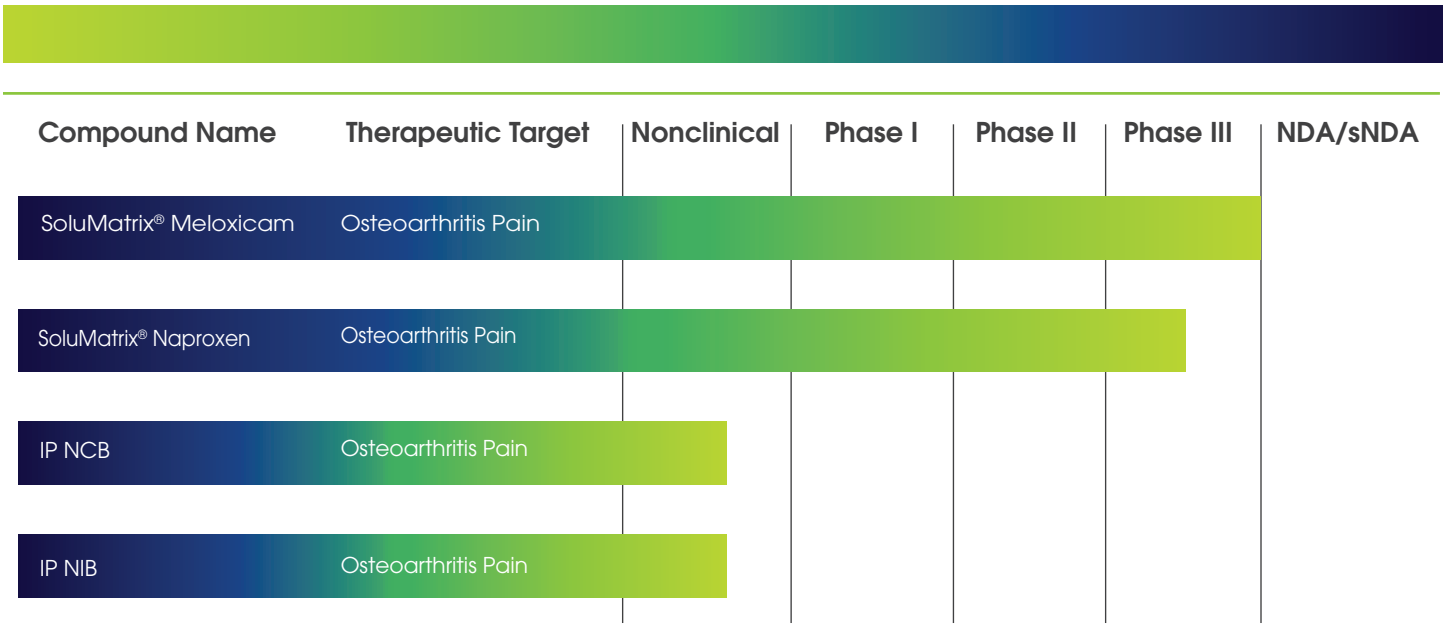
The U.S. Food and Drug Administration (FDA) and a number of professional medical organizations including the American Heart Association, American Gastroenterological Association, and the American College of Rheumatology recommend that NSAIDs be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals[19].

Iroko: *Innovators in Analgesia*

Iroko's portfolio includes ZORVOLEX® (diclofenac) capsules - the first FDA-approved NSAID developed using SoluMatrix Fine Particle Technology™. ZORVOLEX is approved for the management of mild to moderate acute pain and osteoarthritis pain and is now available in pharmacies across the U.S. The second SoluMatrix® NSAID, TIVORBEX™ (indomethacin) capsules, is also FDA-approved for the treatment of mild to moderate acute pain in adults.

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. The safety and efficacy of these investigational products are being evaluated in the therapeutic targets listed.

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 $\geq$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.

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.
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 trademark of iCeutica Pty Ltd and is licensed to Iroko.

Contact:

Jessica Donnelly I For Iroko Pharmaceuticals, LLC I 212-798-9819 I Jessica.Donnelly@cohnwolfe.com

1. Institute of Medicine of the National Academies Report. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, 2011. The National Academies Press, Washington DC (page 55). http://books.nap.edu/openbook.php?record_id=13172&page=55.
2. Institute of Medicine of the National Academies Report. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, 2011. The National Academies Press, Washington DC (page 20) http://books.nap.edu/openbook.php?record_id=13172&page=20.
3. Schnall (2003). Pain Assessment and the Mental Health Practitioner: A Mind-Body Approach. Einstein J. Biol. Med. 20:10-13.
4. American Academy of Pain Medicine. Facts and Figures on Pain. http://www.painmed.org/patientcenter/facts_on_pain.aspx#refer.
5. The American Pain Society. Media Backgrounder. Available at http://www.ampainsoc.org/press/backgrounder.htm. Accessed 8/14/14.
6. Institute of Medicine of the National Academies Report. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, 2011. The National Academies Press, Washington DC. (page 5) http://books.nap.edu/openbook.php?record_id=13172&page=5.
7. Sachs C. (2005 Mar). Oral Analgesics for Acute Nonspecific Pain. Am Fam Physician. 1;71(5):913-918.
8. National Institutes of Health: MedLine Plus. Safely Managing Chronic Pain. Available at http://www.nlm.nih.gov/medlineplus/magazine/issues/spring11/articles/spring11pg4.html. Accessed 8/14/14.
9. Neogi T. et al. (2013 Sep). The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 21(9):1145-53.
10. Medicinal Product Safety. Healthy People. http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=27.
11. Laine L. (2001 Feb). Review Approaches to Nonsteroidal Anti-Inflammatory Drug Use in the High-Risk Patient. Gastroenterology, 120 (3): 594-606.
12. IMS National Prescription Audit, Total Prescriptions, 2009 - 2013.
13. Brooks PM. (1991). Non Steroidal Antiinflammatory Drugs – Differences and Similarities. New England Journal of Medicine. 324:1716-1725.
14. Rhodus NL (1979 May-Jun). Prostaglandins: Promulgators of Pain. Anesth Prog.,26(3): 73–75.
15. ZORVOLEX Prescribing Information 2014, Page 1.
16. 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.
17. Annual Review of Medicine, Nonsteroidal Antiinflammatory Drugs and Renal Function. Vol. 35: 411-428. DOI:10.1146/annurev.med.35.020184.002211.
18. Risser A. (2009 Dec). NSAID Prescribing Precautions. Am Fam Physician. 80(12):1371-1378.
19. U.S. Food and Drug Administration. Public Health Advisory - FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm.