



## **Iroko Pharmaceuticals Receives FDA Approval for VIVLODEX™ - First Low Dose SoluMatrix® Meloxicam for Osteoarthritis Pain**

- ***VIVLODEX Developed to Align with FDA NSAID Recommendations***
- ***Proven Efficacy at Low Doses***

PHILADELPHIA, October 23, 2015 — Iroko Pharmaceuticals, LLC, a global specialty pharmaceutical company dedicated to advancing the science of analgesia, announced today that the United States Food and Drug Administration (FDA) approved VIVLODEX™ (meloxicam) capsules, a nonsteroidal anti-inflammatory drug (NSAID), for the management of osteoarthritis pain in 5 mg and 10 mg doses administered once daily.<sup>1</sup> VIVLODEX is the first FDA-approved low dose SoluMatrix® meloxicam. This marks an important milestone for the 27 million Americans who live with osteoarthritis.<sup>2</sup>

VIVLODEX was developed to align with recommendations from FDA and many professional medical organizations that NSAIDs be used at the lowest effective dose for the shortest possible duration.<sup>3-8</sup> The serious cardiovascular and gastrointestinal adverse events associated with NSAIDs are dose related and risk may occur early in treatment and may increase with duration of use.<sup>9-12</sup> Iroko is committed to addressing these FDA safety recommendations by developing NSAIDs that offer effective pain relief at low doses.

“As recently as July 2015, the FDA announced they would strengthen the existing product label warnings for non-aspirin NSAIDs,<sup>13</sup> further highlighting that NSAIDs should be used at the lowest effective dose for the shortest duration to potentially minimize the risk of adverse events,” said Dr. Byron Cryer, Associate Dean at The University of Texas Southwestern Medical Center. “Meloxicam is the second most commonly prescribed NSAID in the U.S.<sup>14</sup> The approval of VIVLODEX is a welcome option that offers patients an effective, low dose NSAID.”

VIVLODEX, developed using proprietary SoluMatrix Fine Particle Technology™, contains meloxicam as submicron particles that are approximately 10 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution.<sup>15</sup>



“VIVLODEX is Iroko’s third FDA-approved low dose NSAID developed using proprietary SoluMatrix Fine Particle Technology™,” said Osagie Imasogie, Chief Executive Officer and Chairman of the Iroko Board. “Now that we have added a low dose meloxicam product to our growing franchise, we can extend our reach to offer an additional formulation of one of the most commonly used NSAIDs for those affected by osteoarthritis pain,<sup>14</sup> a common cause of disability<sup>2</sup> and the most common type of arthritis.”<sup>16</sup>

FDA approval of VIVLODEX was supported by data from a Phase 3, multi-center, double-blind, placebo-controlled study of 402 patients, aged 40 and older, with pain due to osteoarthritis of the knee or hip, who were randomized to receive treatment with once-daily VIVLODEX 5 mg, VIVLODEX 10 mg, or placebo over a period of 12 weeks. The VIVLODEX doses studied achieved efficacy at 33 percent lower doses than currently available meloxicam products. The New Drug Application (NDA) also included data from a 12-month open-label safety study that enrolled 600 patients.<sup>1,17</sup>

“Research has shown that the use of NSAIDs is likely to increase as the U.S. population continues to age and experience painful conditions that are more common among older adults,”<sup>16</sup> said Dr. Clarence Young, Chief Medical Officer of Iroko Pharmaceuticals. “Patients with osteoarthritis are often treated with NSAIDs for extended periods to manage their pain. For that reason, this approval is important as we continue to expand the number of low dose NSAID options for patients.”

**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  $\geq 2\%$ ) 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. The first SoluMatrix® NSAID is available in pharmacies and a second was approved by FDA and is also available by prescription in the U.S. For more information, visit [www.iroko.com](http://www.iroko.com).

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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.

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<sup>1</sup> VIVLODEX full Prescribing Information. 2015. Iroko Pharmaceuticals, LLC.

<sup>2</sup> Neogi T. et al. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*, 2013 <http://www.ncbi.nlm.nih.gov/pubmed/23973124>.

<sup>3</sup> U.S. Food and Drug Administration. 2005 Public Health Advisory – FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

<sup>4</sup> Antman EM, et al. *Circulation*. 2007;115(12):1634-1642.

<sup>5</sup> Wilcox CM, et al. *Clin Gastroenterol Hepatol*. 2006;4(9):1082-1089.

<sup>6</sup> ACR Ad Hoc Group. *Arthritis Rheum*. 2008;59(8):1058-1073.

<sup>7</sup> Zhang W, et al. *Osteoarthritis Cartilage*. 2008;16(2):137-162.

<sup>8</sup> AGS Panel. *J Am Geriatr Soc*. 2009;57(8):1331-1346.

<sup>9</sup> McGettigan P, et al. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011; 8(9):1-18.

<sup>10</sup> Castellsague J, et al. Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) Project. *Drug Saf*. 2012; 35(12):1127-46.

<sup>11</sup> Helin-Salmivaara A, et al. *Scand J Gastroenterol*. 2007;42(8):923-932.

<sup>12</sup> Helin-Salmivaara A, et al. *Eur Heart J*. 2006;27(14):1657-1663.

<sup>13</sup> U.S. Food and Drug Administration. 2015 Safety Announcement. FDA Strengthens Warning that Non-Aspirin Nonsteroidal Antiinflammatory Drugs (NSAIDs) can Cause Heart Attacks or Strokes.

<sup>14</sup> IMS National Prescription Audit, Total Prescriptions, 2010 - 2014.

<sup>15</sup> Iroko Pharmaceuticals, LLC. Data on file.



<sup>16</sup>The Burden of Musculoskeletal Diseases in the United States: Arthritis and Related Conditions. Chapter 4; 2011. [http://www.boneandjointburden.org/pdfs/BMUS\\_chpt4\\_arthritis.pdf](http://www.boneandjointburden.org/pdfs/BMUS_chpt4_arthritis.pdf).

<sup>17</sup>Altman, R., et al. Lower-Dose SoluMatrix® Meloxicam: Efficacy and Safety in a Phase 3 Study in Adults with Osteoarthritis Pain. Final Poster Presentation for 2014 European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology.