Once-Daily VIVLODEX® for the Management of Osteoarthritis Pain

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Indication

VIVLODEX (meloxicam) capsules are a nonsteroidal anti-inflammatory drug indicated for the management of osteoarthritis (OA) pain.

Important Safety Information

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.

Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
Osteoarthritis (OA) is a debilitating condition of which prevalence increases markedly with age. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the pharmacologic management of OA. In fact, from 2010 through 2014, prescriptions for NSAIDs increased 18% to 120 million, which does not account for over-the-counter (OTC) use. Although NSAIDs are widely used and effective in treating pain associated with OA, it is well established that higher doses of NSAIDs are associated with higher risks for serious gastrointestinal (GI), cardiovascular (CV), and renal risks. To minimize the potential for risk for serious GI and CV events in NSAID-treated patients, the FDA recommends that NSAIDs should be used at the lowest effective dosage for the shortest possible duration.

This monograph provides an overview of OA and the use of NSAIDs in the management of OA. The risk for serious adverse events (AEs) is discussed, including a review of new labeling requirements in regard to the risks for CV events associated with NSAIDs. The need for effective low-dose NSAIDs is examined in the context of SoluMatrix Fine Particle Technology™ as well as the clinical efficacy and safety data of a recently approved NSAID drug product, VIVLODEX® (meloxicam) capsules, for the management of OA pain.

### Overview of OA and NSAIDs

OA is a common, debilitating, degenerative joint disease involving the cartilage and much of its surrounding tissues. Researchers estimate that 26.9 million individuals aged 25 years and older have OA.

OA usually occurs in the hips, knees, shoulders, facet joints, and feet, but can develop in any joint. OA is associated with significant physical and functional limitations as well as psychological comorbidities, including depression and anxiety, leading to large societal and economic burden. In fact, OA of the knee is among the top 5 causes of disability among non-institutionalized adults, with 25% of affected adults unable to perform major activities of daily living.

Although the pathophysiology of OA has long been thought to purely involve mechanical degeneration of the joint, leading to loss of cartilage, evidence now implicates inflammation in disease development and progression. Indeed, the recognition that soluble mediators, such as cytokines or prostaglandins, can lead to more production of matrix metalloproteinases by chondrocytes gave rise to an “inflammatory” theory. Recent experimental data show that subchondral bone also may contribute as a mechanical dampener and...
source of inflammatory mediators that play a role in the OA pain process and degradation of the deep cartilage layer.\textsuperscript{15} Thus, although initially considered cartilage driven, OA—a prototypic age-related disease\textsuperscript{16}—is more complex than previously thought, with low-grade local and systemic inflammation representing the hallmarks of this chronic and progressive condition.\textsuperscript{14,17}

Given the characteristics of OA, NSAIDs, which elicit both analgesic and anti-inflammatory effects, represent a pathophysiologically sound approach to the management of the disease. NSAIDs are among the most commonly used analgesics in the world and often used as first-line medications for joint pain.\textsuperscript{18} Clinical trials have demonstrated the effectiveness of NSAIDs in the treatment of OA.\textsuperscript{19,20} The results of a meta-analysis concluded that NSAIDs are more effective in treating patients with OA pain in the hip or knee relative to acetaminophen.\textsuperscript{20} The American Academy of Orthopaedic Surgeons (AAOS) strongly recommends the use of NSAIDs for the treatment of OA of the knee citing a high level of clinical evidence.\textsuperscript{21} Additionally, current AAOS guidelines do not endorse, nor recommend against, the use of acetaminophen for the treatment of OA of the knee, citing a lack of clinical evidence to support patient improvement compared with placebo.\textsuperscript{21} The American College of Rheumatology conditionally recommends the use of NSAIDs for the treatment of knee, hip, and hand OA,\textsuperscript{2} and the OA Research Society International recommends NSAIDs for the treatment of knee OA for individuals without comorbidities.\textsuperscript{22}

**Limitations and Risks of NSAID Therapy**

NSAID use is associated with adverse reactions, primarily involving the GI tract, CV system, and kidneys.\textsuperscript{5,23-25} Data from observational studies indicate that the risk for serious CV, GI, and renal AEs was associated with NSAID use and is dose related. Higher doses are associated with greater risk for developing these events.\textsuperscript{5-7} More serious GI events include peptic ulcer disease that can lead to life-threatening complications such as bleeding and perforation.\textsuperscript{24} In fact, researchers estimated that more than 100,000 patients with rheumatic disease require hospitalization each year for GI complications associated with NSAID use, and that approximately 16,500 patients die annually from NSAID-related GI complications.\textsuperscript{26} The risks for developing serious GI, CV, and renal AEs are dose related; higher doses increase risk.\textsuperscript{5-7}

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**Figure 2.** Overall systemic exposure for VIVLODEX versus Mobic (meloxicam) in a Phase 1 study of 28 healthy subjects under fasted conditions.

Median time to peak plasma levels occurred earlier for VIVLODEX capsules (2 hours, both 5 and 10 mg) than for meloxicam tablets (4 hours for 15 mg). The clinical relevance of the differences of the pharmacokinetic measurements is unknown. Although the 5-mg dose was not directly compared with Mobic 15 mg, based on dose-proportional pharmacokinetics for VIVLODEX, the overall systemic exposure is 67% less.

Data on file. Iroko Pharmaceuticals, LLC.

Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
Dose-Related Complications With NSAIDs

As previously mentioned, epidemiological studies demonstrate a clear relationship between the dose of NSAIDs and the incidence of serious GI, CV, and renal AEs (Figure 1).5-7 For example, the risk for NSAID-induced GI events (e.g., bleeds, perforation, and ulceration) were shown to be dose related in a population-based cohort study of 958,397 patients (aged 40-79 years) between 1993 and 1998.6 That is, the relative risk (RR) was 2.4 in patients using a low to medium daily NSAID dose versus 4.9 in those using a high daily dose.6

Results from a nested case-control study from The Health Improvement Network database of patients aged 50 to 84 years7 revealed an increase in risk for CV events and increase in daily NSAID dose. The final cohort comprised 716,395 individuals who were followed for approximately 4.1 years.7 Results were adjusted for comorbidities, body mass index, smoking, and the use of concomitant medications.7 The RR was 1.2 in patients using a low to medium daily NSAID dose versus 1.6 in those using a high daily dose.7

Patients are at a greater risk for renal complications with higher daily doses of NSAIDs. A nested case-control study of approximately 400,000 individuals aged 50 to 84 years from the United Kingdom’s General Practice Research Database were evaluated.5 Study participants were free of renal disease, liver cirrhosis, systemic connective tissue disease, and known cancer.5 The RR for developing acute renal failure was 2.5 in patients using a low to medium daily NSAID dose versus 3.4 in those using a high daily dose (35% increase).5 Thus, the accumulated evidence indicates a need for effective low-dose NSAIDs that align with FDA recommendations on NSAID dosing.

NSAID Complications and Duration of Use

Even short-term NSAID therapy places patients at risk, as serious AEs can occur in the first weeks of starting therapy.5,27,28 For example, a matched case-control population-based study of 9,191 cases with upper GI events and 41,780 controls found that the adjusted odds ratio (OR) for upper GI bleeding, ulceration, or perforation was 3.1 in the first 14 days of NSAID use.28 Researchers evaluated the risk for myocardial infarction in a similar matched case-control population-based study and discovered an adjusted OR of 1.4 in the first 14 days of NSAID use.27 Renal complications also can develop shortly after the start of treatment. In fact, data confirm an RR

![Figure 3](https://via.placeholder.com/150)

**Figure 3.** Mean change from baseline in WOMAC pain subscale score at week 12.

Lower scores indicate greater reduction of OA pain.

OA, osteoarthritis; QD, once daily; WOMAC, Western Ontario and McMaster University Osteoarthritis Index

Figure adapted from reference 34.

Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
for acute renal failure of 2.7 in the first 30 days of NSAID therapy. Thus, the accumulated evidence demonstrates an elevated risk for GI, CV, and renal complications even shortly after the initiation of NSAIDs that remains elevated throughout the course of treatment. The prescribing clinician must balance the risks and benefits of NSAID therapy or consider alternative treatment options. The use of NSAIDs at the lowest effective dosage may minimize the risks for developing certain serious AEs. Indeed, the Dosing and Administration section of all oral NSAID prescribing information contains identical wording: “Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.”

FDA Recommendations on NSAID Dosing

The increased risk for serious GI and CV thrombotic events with NSAIDs was first highlighted in the Boxed Warning and Warnings and Precautions sections of NSAID prescription drug labels beginning in 2005. On the basis of a review of new data at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held in February 2014, the FDA strengthened the label warnings that all nonaspirin NSAID formulations elevate risk for heart attack or stroke, and is mandating NSAID label updates for all products. Specifically, the FDA now requires that prescription NSAID labels will be revised to reflect the following information:

- The risk for heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk for heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.

![Figure 4](image)  
**Figure 4.** Responder rates based on change from baseline in WOMAC pain subscale score at week 12.  
QD, once daily; WOMAC, Western Ontario and McMaster University Osteoarthritis Index  
Figure adapted from reference 34.

Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.

- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared with patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk for heart failure with NSAID use.

**Meloxicam: An NSAID for the Treatment of Osteoarthritis Pain**

Meloxicam is an NSAID with anti-inflammatory, analgesic, and antipyretic properties. Like other NSAIDs, its exact mechanism of action is unknown, but it is likely related to inhibition of prostaglandin synthetase (cyclooxygenase). Its pharmacokinetic profile suggests good bioavailability with once-daily dosing.

Meloxicam is commonly prescribed in the United States. Furthermore, its efficacy and safety profile are well established. Like other NSAIDs, meloxicam has been associated with serious GI (eg, bleeding and ulcers of the stomach and intestine) and CV thrombotic events (eg, acute myocardial infarction). Furthermore, like other NSAIDs, most meloxicam prescriptions are written at the highest approved dose.

For example, 77% of prescriptions for meloxicam are at the 15 mg per day dosage. This is despite the FDA recommendations to use the lowest effective NSAID dosage.

**VIVLODEX®: A Recently Approved Low-Dose Meloxicam Drug Product**

Iroko developed a portfolio of low-dose NSAID products to align with FDA recommendations to use the lowest effective dosage. VIVLODEX is an NSAID developed using SoluMatrix Fine Particle Technology to provide efficacy at low doses. This technology reduces particle size to approximately 200 to 800 nm, which increases total surface area. This increased surface area leads to the particles dissolving quickly and rapid absorption into the systemic circulation. Consequently, SoluMatrix Fine Particle Technology alters the pharmacokinetic profile of Iroko’s low-dose NSAIDs.

In a Phase 1 pharmacokinetic study in healthy volunteers (Figure 2) administered single doses of VIVLODEX (5 or 10 mg)

![Figure 5](image)

**Figure 5.** Mean change from baseline in WOMAC function subscale score at week 12.

Lower subscale scores indicate greater improvement.

QD, once daily; WOMAC, Western Ontario and McMaster University Osteoarthritis Index

Figure adapted from reference 34.
under fasted conditions, VIVLODEX capsules demonstrated low systemic exposure with rapid absorption. In comparison with meloxicam 15 mg, the VIVLODEX 10-mg dose provided a 33% lower overall systemic exposure and, based on dose-proportional kinetics, the VIVLODEX 5-mg dose provided a 67% lower systemic exposure. VIVLODEX provides earlier peak plasma levels (2 hours) than meloxicam 15 mg (4 hours), which ensures the drug is available for distribution to tissues.35

**Efficacy and Safety Trials**

**Twelve-Week Efficacy and Safety Study**

The safety and efficacy of VIVLODEX have been examined in clinical trials. A Phase 3, randomized, double-blind, multicenter, parallel-arm, placebo-controlled study compared VIVLODEX 5 or 10 mg taken once daily with placebo for 12 weeks in patients with pain due to OA of the knee or hip. The key inclusion criteria were age 40 years or older, a clinical diagnosis of OA of the knee or hip, radiographic findings grade 2 to 3 (Kellgren-Lawrence), chronic NSAID or acetaminophen use, and a baseline Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain subscale score greater than 40 of 100. The primary efficacy end point was the change from baseline in the WOMAC pain subscale score at week 12.

The study evaluated 402 patients with a mean age of 61 years (range, 40-87 years). Most of the patients were white women; approximately 30% of patients were men. The mean baseline WOMAC pain subscale score across treatment groups was 73 mm using a 0- to 100-mm visual analog scale. VIVLODEX 5 and 10 mg once daily significantly reduced OA pain compared with placebo, as determined by changes in WOMAC pain subscale scores. Mean change from baseline at week 12 was significantly greater in the VIVLODEX 5-mg group (−36.52) and 10-mg group (−34.41) compared with the placebo group (−25.68) (Figure 3). Of the patients in the VIVLODEX 5- and 10-mg groups, 74% and 68% of patients, respectively, achieved at least a 30% improvement in the WOMAC pain subscale score compared with 57.5% of patients taking placebo. Moreover, 59.5% and 57% of patients in the VIVLODEX 5- and 10-mg groups, respectively, achieved at least a 50% improvement in the WOMAC pain subscale score compared with 37% of patients in the placebo group (Figure 4).

**Figure 6.** Mean change from baseline in WOMAC stiffness subscale score at week 12.

Lower scores indicate greater improvement.

QD, once daily; WOMAC, Western Ontario and McMaster University Osteoarthritis Index
Figure adapted from reference 34.
Additionally, efficacy of VIVLODEX was supported by various secondary end points. The mean change from baseline in the WOMAC function subscale score at week 12 was significantly greater in the VIVLODEX 5-mg group (–28.21) and 10-mg group (–28.40) than in the placebo group (–17.95) (Figure 5). Similarly, mean change from baseline in the WOMAC stiffness subscale score at week 12 was significantly greater in the VIVLODEX 5-mg group (–29.68) and 10-mg group (–28.10) than in the placebo group (–18.74) (Figure 6). Finally, a greater proportion of patients treated with VIVLODEX 5 mg (50%) and 10 mg (52.8%) described their condition as “much” or “very much improved” compared with patients receiving placebo (40%) (Table 1).

VIVLODEX was generally well tolerated. The most common adverse reactions (≥2% and more frequent than in the placebo group) observed in this study were diarrhea, nausea, and abdominal discomfort. No deaths or serious AEs occurred during the study period.33,34 The treatment-emergent AEs were generally mild to moderate in severity (Table 2).34

One-Year Open-Label Safety Trial33

The safety of VIVLODEX also was studied in a 1-year, Phase 3, open-label study. This multicenter study evaluated the safety of VIVLODEX 10 mg in 600 patients with pain due to OA of the knee or hip. The patient age ranged from 40 to 86 years.3 Adverse reactions occurring in at least 2% of the safety population are summarized in Table 3.

On October 22, 2015, the FDA approved VIVLODEX for the management of OA pain. The recommended starting dose of VIVLODEX is 5 mg once daily. In patients who require additional analgesia, the dose may be increased to 10 mg per day. Of note, 5 mg is the lowest available FDA-approved dose of meloxicam.36

Conclusion

Osteoarthritis is a common and debilitating condition.1 Additional evidence regarding CV risks associated with nonaspirin NSAIDs have led the FDA to mandate labeling updates for all NSAIDs, including OTC drugs, in regard to the risks for CV events and to continue to recommend use of the lowest effective dose.31 VIVLODEX 5 mg is the lowest dosage unit strength of meloxicam available.36 It provides 67% lower overall systemic exposure and earlier time to peak plasma levels compared with 15 mg of meloxicam, as demonstrated by a pharmacokinetic study in healthy volunteers.35 VIVLODEX provides a clinically significant improvement in pain reduction for patients with OA.34 VIVLODEX is not bioequivalent and therefore not interchangeable with other formulations of oral meloxicam.33

<table>
<thead>
<tr>
<th>Table 1. More Patients Treated With VIVLODEX Reported Their Condition as “Much” or “Very Much Improved” Compared With Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Much/very much improved, %</td>
</tr>
<tr>
<td>Minimally improved, %</td>
</tr>
<tr>
<td>No change, %</td>
</tr>
<tr>
<td>Minimally worse, %</td>
</tr>
<tr>
<td>Much/very much worse, %</td>
</tr>
</tbody>
</table>

QD, once daily
Adapted from reference 34.
Table 2. VIVLODEX Was Generally Well Tolerated in 12-Week Osteoarthritis Clinical Trial

<table>
<thead>
<tr>
<th>Adverse Reactions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>VIVLODEX 5 mg or 10 mg QD (n=269)</th>
<th>Placebo (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea, %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort, %</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> ≥2% in the VIVLODEX group and more frequent than in the placebo group.

QD, once daily

Adapted from reference 33.

Table 3. Adverse Reactions (≥2%) From 52-Week, Phase 3, Open-Label Trial in Patients With Osteoarthritis Pain

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VIVLODEX 10 mg QD (N=600)</th>
<th>VIVLODEX 10 mg QD (N=600)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia, %</td>
<td>6</td>
<td>Nasopharyngitis, %</td>
</tr>
<tr>
<td>Urinary tract infection, %</td>
<td>6</td>
<td>Bronchitis, %</td>
</tr>
<tr>
<td>Osteoarthritis, %</td>
<td>5</td>
<td>Sinusitis, %</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>4</td>
<td>Constipation, %</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>4</td>
<td>Dyspepsia, %</td>
</tr>
<tr>
<td>Headache, %</td>
<td>4</td>
<td>Edema peripheral, %</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4</td>
<td>Nausea, %</td>
</tr>
<tr>
<td>Back pain, %</td>
<td>4</td>
<td>Pain in extremity, %</td>
</tr>
</tbody>
</table>

QD, once daily

Adapted from reference 33.

Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
References


3. Data on file. Iroko Pharmaceuticals, LLC.


33. Full Prescribing Information for VIVLODEX. Iroko Pharmaceuticals, LLC; 2015.


Please see Important Safety Information on page 11 and accompanying full Prescribing Information.
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.
Disclosures: Dr Nalamachu reported that he owns shares of Depomed, KemPharm, and Myoscience, and has served as a consultant, on speakers’ bureaus, and/or has received research support or honoraria from Allergan; AstraZeneca; Collegium Pharmaceutical; Daiichi Sankyo; Depomed; Egalet; INSYS Therapeutics; Ipsen; Iroko Pharmaceuticals, LLC; KemPharm; Mallinckrodt Pharmaceuticals; Myoscience; Purdue Pharma; Recro Pharma; Salix Pharmaceuticals; SCILEX Pharmaceuticals; Sentyr Therapeutics; and Teva Pharmaceuticals.

Dr Pergolizzi reported that he has served as a consultant, on speakers’ bureaus, and/or has received research support or honoraria from AstraZeneca; Daiichi Sankyo; Depomed; Grunenthal; Integra; Iroko Pharmaceuticals, LLC; Mundipharma; and Purdue Pharma.

Dr Fudin reported that he has served as a consultant, and on speakers’ bureaus and advisory boards, for AstraZeneca; Clarity Research; Depomed; Endo Pharmaceuticals; Iroko Pharmaceuticals, LLC; kaléo; KemPharm; Millennium Health; Novartis; SCILEX Pharmaceuticals; and Zogenix.

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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.
VIVLODEX (meloxicam) capsules are indicated for management of osteoarthritis (OA) pain. (1)

HIGHLIGHTS OF PRESCRIBING INFORMATION

VIVLODEX is a non-steroidal anti-inflammatory drug indicated for management of osteoarthritis (OA) pain. (1)

INDICATIONS AND USAGE

VIVLODEX is a non-steroidal anti-inflammatory drug indicated for management of osteoarthritis (OA) pain. (1)

VIVLODEX (meloxicam) Capsules: 5 mg or 10 mg (3)

WARNINGS AND PRECAUTIONS

VIVLODEX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)

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. (5.2)

DOSAGE FORMS AND STRENGTHS

VIVLODEX (meloxicam) Capsules: 5 mg or 10 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to meloxicam or any components of the drug product (4)

History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)

In the setting of CABG surgery (4)

Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)

Gastrointestinal (GI) Bleeding, Ulceration, and Perforation

Heart Failure and Edema: Avoid use of VIVLODEX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of VIVLODEX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.8)

Analgesic Reactions: Seek emergency help if an analgesic reaction occurs (5.7)

Exacerbation of Asthma Related to Aspirin Sensitivity: VIVLODEX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)

Serious Skin Reactions: Discontinue VIVLODEX at first appearance of skin rash or other signs of hypersensitivity (5.9)

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)

Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2% in controlled clinical trials of VIVLODEX 5 mg or 10 mg group) are diarrhea, nausea, abdominal discomfort. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Iroko Pharmaceuticals, LLC at 1-877-757-0676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRI’s/SNRIs); Monitor patients for bleeding who are concomitantly taking VIVLODEX with drugs that interfere with hemostasis. Concomitant use of VIVLODEX and analgesic doses of aspirin is not generally recommended (7)

ACE inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers; Concomitant use with VIVLODEX may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

ACE inhibitors and ARBs: Concomitant use with VIVLODEX in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In high risk patients, monitor for signs of worsening renal function (7)

Diuretics; NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)

Digoxin: Concomitant use with VIVLODEX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of VIVLODEX in women who have difficulties conceiving (8.3)

INDICATIONS AND USAGE

VIVLODEX is indicated for management of osteoarthritis pain. (1)

DOSE AND ADMINISTRATION

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

For management of osteoarthritis pain, the recommended starting dosage is 5 mg orally once daily. Dose may be increased to 10 mg in patients who require additional analgesia. The maximum recommended daily oral dose of VIVLODEX is 10 mg.

In patients on hemodialysis, the maximum daily dosage is 5 mg [see Warnings and Precautions (5.6), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Non-Interchangeability with Other Formulations of Meloxicam

VIVLODEX capsules have not shown equivalent systemic exposure to other formulations of oral meloxicam. Therefore, VIVLODEX capsules are not interchangeable with other formulations of oral meloxicam even if the total milligram strength is the same. Do not substitute similar dose strengths of other meloxicam products [see Clinical Pharmacology (12.3)].

DOSE FORMS AND STRENGTHS

VIVLODEX (meloxicam) capsules: 5 mg – light pink body with a dark blue cap (imprinted IP-205 on the body and 5 mg on the cap in white ink).

VIVLODEX (meloxicam) capsules: 10 mg – pink body and a dark blue cap (imprinted IP-206 on the body and 10 mg on the cap in white ink).

CONTRAINDICATIONS

VIVLODEX is contraindicated in the following patients:

Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product [see Warnings and Precautions (5.7, 5.9)]

History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Warnings and Precautions (5.7, 5.8)]

In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]
5
5.1 Cardiovascular Thrombotic Events
Clinical trials of several COX-2-selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been highest consistently at doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as meloxicam, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs, including meloxicam, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with VIVLODEX. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include longer duration of therapy, use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize GI Risk in NSAID-Treated Patients
- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For high risk patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue VIVLODEX until the serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity
Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including meloxicam. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms suggestive or indicative disease develop, or if symptoms manifestations of acute liver disease (e.g., deranged aminotransferases, rash, etc.), discontinue VIVLODEX immediately, and perform a clinical evaluation of the patient.

5.4 Hypersensitivity
NSAIDs, including VIVLODEX, can lead to new onset or worsening of pre-existing hypersensitivity, either of which may contribute to the increased incidence of CV events. Patients taking aspirin can develop enzyme (Acetyl-CoA carboxylase) and/or non-steroidal anti-inflammatory drug (NSAID) hypersensitivity. When taking NSAIDs [see Drug Interactions (7)].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema
The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2-selective treated- patients compared to placebo-treated patients and compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of meloxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid the use of VIVLODEX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If VIVLODEX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy was usually followed by recovery to the pretreatment state.

New information is available from controlled clinical studies regarding the use of VIVLODEX in patients with advanced renal disease. The renal effects of VIVLODEX may hasten the progression of renal dysfunction in patients with pre-existing renal disease. Correct volume status in dehydrated and hypovolemic patients prior to initiating VIVLODEX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of VIVLODEX [see Drug Interactions (7)]. Avoid the use of VIVLODEX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If VIVLODEX CV effects are observed in patients with advanced renal disease, monitor patients for signs of worsening renal function.

5.7 Anaphylactic Reactions
Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma [see Contraindications (4), Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subset population of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VIVLODEX is contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When VIVLODEX is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of VIVLODEX at the first appearance of skin rash or any other sign of hypersensitivity. VIVLODEX is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus
Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIVLODEX, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.1)].

5.11 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect upon erythropoiesis. If a patient treated with VIVLODEX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including VIVLODEX, may increase the risk of bleeding events. Concomitant use of warfarin and other anticoagulants, antplatelet agents (e.g., aspirin), and serotonin reuptake inhibitors (SSRIs) and selective serotonin reuptake inhibitors (SSRIs) may increase this risk. Monitor these patients for signs of bleeding [Drug Interactions (7)].

5.12 Masking of Inflammation and Fever
The pharmacological activity of VIVLODEX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring
Because serious GI bleeding, hematotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovacular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration and Perforation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypersensitivity [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.5)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.9)]
- Hematologic Toxicity [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Osteoarthritis Pain
Eight hundred sixty-eight (868) patients with osteoarthritis pain, ranging in age from 40 – 87 years, were enrolled in two Phase 3 clinical trials and received VIVLODEX 5 mg or 10 mg once daily. Fifty percent (50%) of patients were aged 61 years or older. Two hundred sixty-nine (269) patients received VIVLODEX 5 mg or 10 mg once daily in the 12-week, double-blind, placebo-controlled, clinical trial of osteoarthritis pain of the knee or hip. The most frequent
adverse reactions in this study are summarized in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VIVLODEX 5 mg or 10 mg N=269</th>
<th>Placebo N=133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal Discomfort</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Six hundred (600) patients received VIVLODEX 10 mg once daily in a 52-week, open-label, clinical trial in osteoarthritis pain of the knee or hip. Of these, 390 (65%) patients completed the trial. The most frequent adverse reactions in this study are summarized in Table 2.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VIVLODEX 10 mg N=600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>6%</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>4%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>2%</td>
</tr>
</tbody>
</table>

Additional adverse reactions reported for meloxicam:
- **Body as a Whole**: allergic reaction, face edema, fatigue, fever, hot flashes, malaise, syncope, weight decrease, weight increase
- **Cardiovascular**: angina pectoris, cardiac failure, hypertension, hypotension
- **Central and Peripheral Nervous System**: convulsions, paresthesia, tremor, vertigo
- **Gastrointestinal**: colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastritis, gastrointestinal hemorrhage, hematemia, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative
- **Heart Rate and Rhythm**: arrhythmia, palpitation, tachycardia
- **Hematologic**: agranulocytosis, leukenemia, purpura, thrombocytopenia
- **Immune System**: anaphylactoid reactions (including shock)
- **Liver and Biliary System**: ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, jaundice, liver failure
- **Metabolic and Nutritional**: dehydratation
- **Psychiatric**: abnormal dreaming, alterations in mood (such as mood elevation), anxiety, appetite increased, confusion, depression, nervousness, somnolence
- **Respiratory**: asthma, bronchospasm, dyspnea
- **Skin and Appendages**: alopecia, angiodema, bullous eruption, erythema multiforme, exfoliative dermatitis, photosensitivity reaction, pruritus, Stevens-Johnson Syndrome, toxic epidermal necrolysis, sweating increased, urticaria
- **Special Senses**: abnormal vision, conjunctivitis, taste perversion, tinnitus
- **Urinary System**: albuminuria, acute urinary retention, BUN increased, creatinine increased, hematuria, interstitial nephritis, renal failure

7 DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with meloxicam.

### Drugs That Interfere with Hemostasis

**Clinical Impact:**
- Meloxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants has increased risk of serious bleeding compared to either drug alone.
- Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.

**Intervention:**
- Monitor patients with concomitant use of VIVLODEX with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.11)].

### Drug Interactions with Meloxicam

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>INTERACTION</strong></th>
<th><strong>IMPACT</strong></th>
<th><strong>CONSIDERATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)]. VIVLODEX is not a substitute for aspirin for cardiovascular prophylaxis.</td>
<td></td>
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</tr>
<tr>
<td><strong>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers</strong></td>
<td>• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).</td>
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</tr>
<tr>
<td></td>
<td>• In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.</td>
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<tr>
<td></td>
<td>• During concomitant use of VIVLODEX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>The concomitant use of meloxicam with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.</td>
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</tr>
<tr>
<td></td>
<td>• During concomitant use of VIVLODEX and digoxin, monitor serum digoxin levels.</td>
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<td></td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td>NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.</td>
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<tr>
<td></td>
<td>• During concomitant use of VIVLODEX and lithium, monitor patients for signs of lithium toxicity.</td>
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<tr>
<td><strong>Methotrexate</strong></td>
<td>Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).</td>
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</tr>
<tr>
<td></td>
<td>• During concomitant use of VIVLODEX and methotrexate, monitor patients for methotrexate toxicity.</td>
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<td></td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>Concomitant use of VIVLODEX and cyclosporine may increase cyclosporine’s nephrotoxicity.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• During concomitant use of VIVLODEX and cyclosporine, monitor patients for signs of worsening renal function.</td>
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<td></td>
</tr>
<tr>
<td><strong>NSAIDs and Saliylates</strong></td>
<td>Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salicylate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)].</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The concomitant use of meloxicam with other NSAIDs or salicylates is not recommended.</td>
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</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td>Concomitant use of VIVLODEX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).</td>
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<tr>
<td></td>
<td>• During concomitant use of VIVLODEX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
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<td></td>
<td>• NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed.</td>
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<tr>
<td></td>
<td>• In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.</td>
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</tbody>
</table>

### Clinical Use in Specific Populations

#### 8.1 Pregnancy

**Risk Summary:**
- Use of NSAIDs, including VIVLODEX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIVLODEX, in pregnant women starting at 30 weeks of gestation (third trimester).
- There are no adequate and well-controlled studies of VIVLODEX in pregnant women.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss.
In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 1- and 10-times, respectively, the maximum recommended human dose (MRHD) of VIVLODEX. Increased incidence of septal heart defects were observed in rabbits treated throughout organogenesis with meloxicam at an oral dose equivalent to 116-times the MRDD. In pre- and post-natal reproduction studies, increased incidence of dystocia, delayed parturition, and decreased offspring survival were observed in rats treated with meloxicam at an oral dose equivalent to 0.125 times the MRDD of VIVLODEX. No teratogenic effects were observed in rats treated with meloxicam during organogenesis at an oral dose equivalent to 3.9-fold the MRDD [See Data].

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as meloxicam, resulted in increased pre- and post-partum implantation loss. Clinical Considerations

Labor or Delivery

There are no studies on the effects of VIVLODEX during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal data

Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (3.9-times the maximum recommended daily dose [MRDD] of 10 mg of VIVLODEX based on body surface area [BSA] comparison). Administration of meloxicam to pregnant rabbits throughout organogenesis did not result in an increased incidence of fetal malformations; however, decreased offspring survival was observed in rats treated with meloxicam at an oral dose equivalent to 0.125-times the MRDD of VIVLODEX. No teratogenic effects were observed in rats treated with meloxicam during organogenesis at an oral dose equivalent to 3.9-times the MRDD [See Data].

No dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. Because meloxicam is significantly metabolized in the liver, use VIVLODEX in patients with severe hepatic impairment only if the benefits are expected to outweigh the risks. If VIVLODEX is used in patients with severe hepatic impairment, monitor patients for signs of worsening liver function [see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of VIVLODEX in subjects with severe renal impairment is not recommended. In a previous study, the free Cmax plasma concentrations following a single dose of meloxicam with renal impairment (creatinine clearance 15-30 mL/min) compared to healthy volunteers (3.3% free fraction). Therefore, the maximum VIVLODEX dosage in this population is 5 mg per day. Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

OVERDOSAGE

Symptoms following acute NSAID overdosage have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but are rare [see Warnings and Precautions (5.1, 5.2, 5.3)]. There is limited experience with meloxicam overdose. In four reported cases of meloxicam overdose, patients took 6 to 11 times the highest available dose of meloxicam tablets (15 mg); all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

Renal impairment: Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all patients.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

VIVLODEX (meloxicam) capsules are a nonsteroidal anti-inflammatory drug, available as pink and blue capsules containing 5 mg or 10 mg for oral administration. The chemical name is 4-hydroxy-2-(ethyl-6-furfuryl)-4-[(E)-5-(2-thiazolyl)pentamethylene]-2-carboxamide-1,1-dioxide. The molecular weight is 354.1. Its molecular formula is C20H21N2O3S, and it has the following chemical structure:

\[
\text{C}_{20}\text{H}_{21}\text{N}_{2}\text{O}_{3}\text{S}
\]

Meloxicam is a pale yellow solid, pracystically insoluble in water, with high solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P) of 3.5. In n-octanol-buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.

The inactive ingredients in VIVLODEX include: lactose monohydrate, sodium lauryl sulfate, sodium starch, stearic acid, microcrystalline cellulose, and croscarmellose sodium. The capsule shells contain gelatin, titanium dioxide, and dyes FD&C blue #2, FD&C red #40, FD&C yellow #6, and carmine. The imprinting on the gelatin capsule is white edible ink. The 5 mg capsules have a light pink body with “IP-205” imprinted in white ink and a dark blue cap with “5 mg” imprinted in white ink. The 10 mg capsules have a light pink body with “IP-206” imprinted in white ink and a dark blue cap with “10 mg” imprinted in white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIVLODEX is an anti-inflammatory, and antipyretic properties. The mechanism of action of VIVLODEX, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis in vitro. Meloxicam concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

The relative bioavailability of VIVLODEX 10 mg capsules compared to meloxicam 15 mg tablets was assessed in 28 healthy subjects under fasted and fed conditions in a single-dose crossover study. VIVLODEX 10 mg capsules did not result in an equivalent systemic exposure compared to 15 mg meloxicam tablets. When taken under fasted conditions, a 33% lower dose of meloxicam in VIVLODEX 10 mg capsules resulted in a 33% lower overall systemic exposure (AUCinf), and a comparable mean peak plasma concentration (Cmax) to meloxicam 15 mg tablets. The median time to maximum plasma concentration (Tmax) occurred earlier for VIVLODEX capsules (2 hours for both 5 mg and 10 mg) than for meloxicam tablets (4 hours for 15 mg).

Absorption

Single oral doses of VIVLODEX 5 mg and 10 mg were associated with dose-proportional pharmacokinetics. Maximal plasma concentrations were reached within 2 hours post-dose for both VIVLODEX 5 mg and 10 mg capsules when taken under fasted conditions. A second meloxicam concentration peak occurs around 8 hours post-dose.

Taking VIVLODEX with food causes a decrease in the rate but not the overall extent of systemic meloxicam absorption compared with taking VIVLODEX on an empty stomach. VIVLODEX capsules administered under fed conditions results in 22% lower mean Cmax, and a 3 hour delay in median Tmax (15 hours for fed versus 2 hours for fasting) compared to the fasted condition. Significant changes in AUC were not observed. VIVLODEX can be administered without regard to timing of meals.

Distribution

The mean volume of distribution (V) of meloxicam is approximately 10 L. Meloxicam is >99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases slightly as total doses increase. Meloxicam is an inhibitor of renal disease. Prostaglandin was identified in the plasma of some dose-limiting factors in the induction of pain.

Absorption

Following a single oral dose of VIVLODEX 5 mg and 10 mg, meloxicam is absorbed rapidly with peak plasma concentrations (Cmax) occurring at 2 hours (Tmax).

There is significant biliary and/or enteral secretion of the drug. This is less than 10%.

Meloxicam is not dialyzable. There is no evidence of metabolism. Meloxicam is moderately bound to human plasma proteins (primarily albumin). Drug binding is independent of drug concentration, over the clinically relevant concentration range, but decreases slightly as total doses increase. Meloxicam is an inhibitor of renal disease.

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5’-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate metabolite 5’-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). In vitro studies indicate that CYP2C8 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients’’’”’and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%. The mean elimination half-life (t1/2) for VIVLODEX 5 mg and 10 mg is approximately 22 hours.

Specific Populations

Pediatric: The pharmacokinetics of VIVLODEX have not been investigated in pediatric patients.

Hepatic Impairment: Following a single 15 mg dose of meloxicam tablets there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [see Warnings and Precautions (5.3), Use in Specific Populations (8.6)].

Renal Impairment: Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all
groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary for patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of VIVLODEX in subjects with severe renal impairment is not recommended.

Following a single dose of meloxicam, the free Cmax plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable [see Warnings and Precautions (5.6), Use in Specific Populations (8.7)].

Drug Interactions

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 clinically significant drug interactions of NSAIDs with aspirin [see Drug Interactions (7)].

Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This result occurred in a decrease in t1/2 from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established [see Drug Interactions (7)].

Cimetidine: Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Digoxin: Meloxicam tablets 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after 8-acetyldigoxin administration for 7 days at clinical doses. In vitro testing found no protein binding drug interaction between digoxin and meloxicam [see Drug Interactions (7)].

Lithium: In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam tablets 15 mg once per day every day as compared to subjects receiving lithium alone [see Drug Interactions (7)].

Methotrexate: A previous study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. In vitro, methotrexate did not displace meloxicam from human serum protein binding sites [see Drug Interactions (7)].

Warfarin: The effect of meloxicam tablets on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering VIVLODEX with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced [see Drug Interactions (7)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

There is no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) and mice (92 weeks). Oral administration of meloxicam at oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.8- and 3.9-times, respectively, the maximum recommended daily dose (MRDD) of 10 mg of VIVLODEX based on body surface area (BSA) comparison).

Mutagenesis

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and in an vivo micronucleus test in mouse bone marrow.

Impairment of Fertility

In previous studies of meloxicam, there was no impairment of male or female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 8.7 and 4.8-times, respectively, the MRDD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Osteoarthritis Pain

The efficacy of VIVLODEX in the management of osteoarthritis pain was demonstrated in a randomized, double-blind, multicenter, parallel-arm, placebo-controlled study comparing VIVLODEX 5 mg or 10 mg taken once daily and placebo in patients with pain due to osteoarthritis of the knee or hip. The study evaluated 402 patients with a mean age of 61 (range 40 to 87 years). Osteoarthritis pain was measured using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Pain Subscale. The mean baseline WOMAC Pain Subscale Score across treatment groups was 73 mm using a 0 to 100 mm visual analog scale.

The primary efficacy endpoint was the change from baseline to Week 12 in the WOMAC Pain Subscale Score. VIVLODEX 5 mg and 10 mg once daily significantly reduced osteoarthritis pain compared with placebo, as measured by changes in WOMAC Pain Subscale Scores. Although both the 5 mg and 10 mg doses significantly reduced pain compared to placebo, the proportion of responders achieving various percentage reductions in pain intensity from baseline to Week 12 is similar for both the 5 mg and 10 mg once daily doses. The proportion (%) of patients in each group who demonstrated reduction in their pain intensity score from baseline to Week 12 is shown in Figure 1. The figure is cumulative, so patients whose change from baseline is, for example, 30%, are also included in every level of pain reduction below 30%. Patients who did not complete the study were classified as non-responders.

Figure 1

Proportion (%) of Patients Achieving Various Percentage Reductions in Pain Intensity from Baseline to Week 12

16 HOW SUPPLIED/STORAGE AND HANDLING

VIVLODEX (meloxicam) capsules are supplied as:

- 5 mg - light pink body and dark blue cap (imprinted IP-205 on the body and 5 mg on the cap in white ink)
  NDC (42211-205-23), Bottles of 30 capsules
  NDC (42211-205-29), Bottles of 90 capsules

- 10 mg - pink body and dark blue cap (imprinted IP-206 on the body and 10 mg on the cap in white ink)
  NDC (42211-206-23), Bottles of 30 capsules
  NDC (42211-206-29), Bottles of 90 capsules

Storage

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store in the original container and keep the bottle tightly closed to protect from moisture. Dispense in a tight container if package is subdivided.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Patients, families, or their caregivers should be informed of the following information before initiating therapy with VIVLODEX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcers and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop VIVLODEX and seek immediate medical therapy [see Warnings and Precautions (5.3)].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including unexplained shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4), Warnings and Precautions (5.7)].

Serious Skin Reactions

Advise patients to stop VIVLODEX immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9)].

Fetal Toxicity

Inform pregnant women to avoid use of VIVLODEX and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10)]. Use in Specific Populations (8.1).

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of VIVLODEX with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2), Drug Interactions (7)]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with VIVLODEX until they talk to their healthcare provider [see Drug Interactions (7)].

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Issued: October/2015
WUS-2910151224
The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol

NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?
Do not take NSAIDs:
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy.
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”
- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs
- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued or Revised: October 2015

VLUS-2910151224