HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIVORBEX® safely and effectively. See full prescribing information for TIVORBEX.

TIVORBEX (indomethacin) Capsules, for oral use
Initial U.S. Approval 1965

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular 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 (5.1)**
- **TIVORBEX 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)**

RECENT MAJOR CHANGES

Warnings and Precautions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (5.10),	04/2021
Warnings and Precautions, Fetal Toxicity (5.11)	04/2021

INDICATIONS AND USAGE

TIVORBEX is a nonsteroidal anti-inflammatory drug indicated for treatment of mild to moderate acute pain in adults (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- The dosage is 20 mg orally three times daily or 40 mg orally two or three times daily. (2.1)
- TIVORBEX capsules are not interchangeable with other formulations of oral indomethacin (2.2)

DOSAGE FORMS AND STRENGTHS

TIVORBEX (indomethacin) Capsules: 20 mg and 40 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to indomethacin 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)

WARNINGS AND PRECAUTIONS

- 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)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of TIVORBEX 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 TIVORBEX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: TIVORBEX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue TIVORBEX at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including TIVORBEX, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2% in TIVORBEX 20 mg and 40 mg groups) are nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, constipation, pruritus, diarrhea, dyspepsia, post procedural swelling, presyncope, rash, abdominal pain (upper), somnolence, pruritus generalized, hyperhidrosis, decreased appetite, hot flush and syncope. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharm-Olam at 1-800-511-6754 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking TIVORBEX with drugs that interfere with hemostasis. Concomitant use of TIVORBEX and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with TIVORBEX may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with TIVORBEX in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such 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 TIVORBEX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular 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 [*see Warnings and Precautions (5.1)*].**
- **TIVORBEX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].**

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 [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of TIVORBEX and other treatment options before deciding to use TIVORBEX. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

For treatment of mild to moderate acute pain, the dosage is 20 mg three times daily or 40 mg two or three times daily.

2.2 Non-Interchangeability with Other Formulations of Indomethacin

Different dose strengths and formulations of oral indomethacin are not interchangeable. This difference should be taken into consideration when changing strengths or formulations.

3 DOSAGE FORMS AND STRENGTHS

TIVORBEX (indomethacin) Capsules 20 mg – dark blue body and light blue cap (imprinted IP-201 on the body and 20 mg on the cap in white ink).

TIVORBEX (indomethacin) Capsules 40 mg – dark blue body and blue cap (imprinted IP-202 on the body and 40 mg on the cap in white ink).

4 CONTRAINDICATIONS

TIVORBEX is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin 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 WARNINGS AND PRECAUTIONS

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 observed most consistently at higher 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 indomethacin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in

NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of TIVORBEX in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If TIVORBEX is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including indomethacin, 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 NSAIDs. 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 of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant 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 the GI Risks 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 such 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 TIVORBEX until a 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 indomethacin.

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 consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TIVORBEX immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including TIVORBEX, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies 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 and nonselective NSAID-treated patients 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 indomethacin 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 TIVORBEX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If TIVORBEX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

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 is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of TIVORBEX in patients with advanced renal disease. The renal effects of TIVORBEX may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating TIVORBEX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of TIVORBEX [*see Drug Interactions (7)*]. Avoid the use of TIVORBEX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If TIVORBEX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

It has been reported that the addition of the potassium-sparing diuretic, triamterene, to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Hyperkalemia
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Both indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.

5.7 Anaphylactic Reactions

Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation 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, TIVORBEX is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When TIVORBEX 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 indomethacin, 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 TIVORBEX at the first appearance of skin rash or any other sign of hypersensitivity.

TIVORBEX is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as TIVORBEX. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalties, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involoved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue TIVORBEX and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including TIVORBEX, in pregnant women at about 30 weeks gestation and later. NSAIDs, including TIVORBEX, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including TIVORBEX, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit TIVORBEX use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic flude if TIVORBEX treatment extends beyond 48 hours. Discontinue TIVORBEX if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1*)]

5.12 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 on erythropoiesis. If a patient treated with TIVORBEX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including TIVORBEX, may increase the risk of bleeding events. Co-morbid conditions, such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and

serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.13 Masking of Inflammation and Fever

The pharmacological activity of TIVORBEX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, 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)*].

5.15 Central Nervous System Effects

TIVORBEX may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue TIVORBEX if severe CNS adverse reactions develop.

TIVORBEX may cause drowsiness; therefore, caution patients about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with TIVORBEX.

5.16 Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with TIVORBEX. Be alert to the possible association between the changes noted and TIVORBEX. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. TIVORBEX is not indicated for long-term treatment.

6 ADVERSE REACTIONS

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

- Cardiovascular 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)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.12)*]

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 clinical practice.

Five hundred and fifty-four patients (554) received TIVORBEX 20 mg or 40 mg for up to 48 hours in two double-blind, placebo-controlled, clinical trials of acute pain following bunionectomy. The most frequent adverse reactions in these trials are summarized below.

Table 1 Summary of Adverse Reactions (≥2% in TIVORBEX 20 mg or 40 mg group) - Phase 3 Studies in Patients With Postsurgical Pain

Any Treatment Emergent AE	TIVORBEX 40 mg three times daily* (%) N=187	TIVORBEX 40 mg twice daily* (%) N=184	TIVORBEX 20 mg three times daily* (%) N=183	Placebo* (%) N=188
Nausea	33	33	34	36
Post procedural edema	24	22	26	32
Headache	16	14	11	11
Dizziness	15	14	10	17
Vomiting	8	10	12	11
Post procedural hemorrhage	5	11	5	6
Constipation	4	5	6	5
Pruritus	2	3	4	0
Diarrhea	2	3	2	1
Dyspepsia	3	2	1	1
Post procedural swelling	1	3	1	1
Presyncope	2	3	1	2
Rash	2	1	2	0
Abdominal pain, upper	2	1	2	1
Somnolence	2	2	1	1
Pruritus generalized	1	2	1	0
Hyperhidrosis	0	2	1	1
Decreased appetite	0	2	1	1
Hot flush	0	1	2	1
Syncope	0	2	1	1

*One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as rescue medication for pain management. There was a greater use of concomitant opioid rescue medication in placebo-treated patients than in TIVORBEX-treated patients *[see Clinical Studies (14)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of indomethacin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

***Gastrointestinal*:** anorexia**,** bloating (includes distension)**,** flatulence**,** peptic ulcer**,** gastroenteritis**,** rectal bleeding**,** proctitis**,** single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines intestinal ulceration associated with stenosis and obstruction, gastrointestinal bleeding without obvious

ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc) development of ulcerative colitis and regional ileitis ulcerative stomatitis**,** toxic hepatitis and jaundice (some fatal cases have been reported)**,** intestinal strictures (diaphragms), pancreatitis.

Cardiovascular: hypertension, hypotension, tachycardia, chest pain, congestive heart failure, arrhythmia, palpitations.

Hematologic: leukopenia, bone marrow depression, anemia secondary to obvious or occult gastrointestinal bleeding, aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenic purpura, disseminated intravascular coagulation.

Central Nervous System: anxiety (includes nervousness)**,** muscle weakness**,** involuntary muscle movements**,** insomnia**,** confusion**,** psychic disturbances including psychotic episodes, mental confusion, drowsiness, light-headedness, syncope, paresthesia, aggravation of epilepsy and parkinsonism, depersonalization, coma, peripheral neuropathy, convulsion, dysarthria.

Hypersensitivity: acute anaphylaxis**,** acute respiratory distress rapid fall in blood pressure resembling a shock-like state**,** angioedema**,** dyspnea**,** asthma**,** purpura**,** angiitis**,** pulmonary edema**,** fever.

Metabolic: edema**,** weight gain**,** fluid retention**,** flushing or sweating**,** hyperglycemia**,** glycosuria**,** hyperkalemia

Genitourinary: hematuria, vaginal bleeding, proteinuria, nephrotic syndrome, interstitial nephritis: BUN elevation, renal insufficiency, including renal failure.

Special Senses: ocular — corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin; blurred vision, diplopia, hearing disturbances, deafness.

Skin and Appendages: pruritus**,** rash, urticaria**,** petechiae or ecchymosis**,** exfoliative dermatitis**,** erythema nodosum**,** loss of hair**,** Stevens-Johnson syndrome**,** erythema multiforme**,** toxic epidermal necrolysis.

Miscellaneous: epistaxis**,** breast changes, including enlargement and tenderness**,** gynecomastia

Causal relationship unknown

Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Cardiovascular: Thrombophlebitis

Hematologic: Although there have been several reports of leukemia, the supporting information is weak

Genitourinary: Urinary frequency

Musculoskeletal and Connective Tissue: A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group Ab hemolytic streptococcus, has been described in persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome [*see Warnings and Precautions (5.9)*].

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with indomethacin.

Table 2 Clinically Significant Drug Interactions with Indomethacin

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of 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 TIVORBEX 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 (5.12)*].
Aspirin	
Clinical Impact:	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)*].
Intervention:	Concomitant use of TIVORBEX and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. TIVORBEX is not a substitute for low dose aspirin for cardiovascular protection
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • 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.
Intervention:	• During concomitant use of TIVORBEX and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of TIVORBEX and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	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. It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

	Both indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently [*see Warnings and Precautions* (5.6)].
Intervention:	Indomethacin and triamterene should not be administered together. During concomitant use of TIVORBEX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of TIVORBEX and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	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.
Intervention:	During concomitant use of TIVORBEX and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of TIVORBEX and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of TIVORBEX and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of TIVORBEX and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*]. Combined use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin. [see *Clinical Pharmacology (12.3)*]. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage.
Intervention:	The concomitant use of indomethacin with other NSAIDs or salicylates , especially diflunisal, is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of TIVORBEX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of TIVORBEX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. 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. 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.
Probenecid	
Clinical Impact	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.
Intervention	During the concomitant use of TIVORBEX and probenecid, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Effects on Laboratory Tests

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including TIVORBEX, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of TIVORBEX use between about 20 and 30 weeks of gestation, and avoid TIVORBEX use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including TIVORBEX, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

OligohydramniosNeonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

There are no adequate and well-controlled studies of TIVORBEX 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 animal reproduction studies, retarded fetal ossification was observed with administration of indomethacin to mice and rats during organogenesis at doses 0.16 and 0.32 times, respectively, the maximum recommended human dose (MRHD, 120 mg). In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.2 times the MRHD. When rat and mice dams were dosed during the last three days of gestation, indomethacin produced neuronal necrosis in the offspring at 0.1 and 0.05 times the MRHD, respectively [*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 indomethacin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including TIVORBEX, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If TIVORBEX treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue TIVORBEX and follow up according to clinical practice (*see Data*).

Labor or Delivery

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

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequenty reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Data

Animal data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.16 times [mice] and 0.32 times [rats] the MRHD on a mg/m^2 basis, respectively) considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.20 to 0.60 times MRHD on a mg/m^2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations.

In rats and mice, maternal indomethacin administration of 4.0 mg/kg/day (0.32 and 0.16 times the MRHD on a mg/m^2 basis) during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups (0.16 and 0.08 times the MRHD on a mg/m^2 basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.

8.2 Lactation

Risk Summary

Based on available published clinical data, indomethacin may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the breastfed infant from the TIVORBEX or from the underlying maternal condition.

Data

In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight-adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including TIVORBEX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including TIVORBEX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

The safety and effectiveness of TIVORBEX in pediatric patients 17 years of age and younger has not been established.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*].

Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.1)];* physicians should remain alert to the possibility of such adverse effects in the elderly.

Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient population, and it may be useful to monitor renal function [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

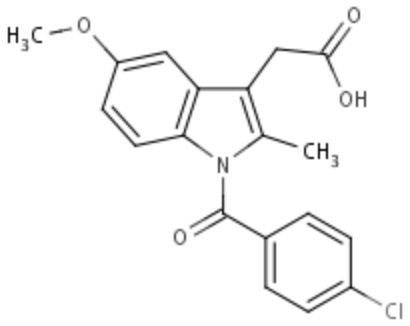
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4,5.6)*].

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

11 DESCRIPTION

TIVORBEX (indomethacin) capsule is a nonsteroidal anti-inflammatory drug, available as hard gelatin capsules of 20 mg and 40 mg for oral administration. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The molecular weight is 357.8. Its molecular formula is $C_{19}H_{16}ClNO_4$, and it has the following chemical structure.



Indomethacin is a white to yellow crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. Indomethacin has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.

The inactive ingredients in TIVORBEX include: lactose monohydrate, sodium lauryl sulfate, microcrystalline cellulose, croscarmellose sodium and sodium stearyl fumarate. The capsule shells contain gelatin, titanium dioxide, and dyes FD&C blue #1, FD&C blue #2 and FD&C red #40. The imprinting on the gelatin capsules is white edible ink. The 20 mg capsules have a dark blue body imprinted with IP-201 and light blue cap imprinted with 20 mg in white ink. The 40 mg capsules have a dark blue body imprinted with IP-202 and blue cap imprinted with 40 mg in white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Indomethacin has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of TIVORBEX, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin 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 indomethacin 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 TIVORBEX 40 mg capsules was compared to indomethacin immediate-release (IR) capsules 50 mg in 38 healthy subjects under fasted conditions in a single-dose crossover study.

TIVORBEX (indomethacin) 40 mg capsules do not result in an equivalent systemic exposure to 50 mg indomethacin IR capsules.

When taken under fasted conditions, a 20% lower dose of indomethacin in TIVORBEX 40 mg capsules resulted in a 21% lower mean systemic exposure (AUC_{inf}) and an equivalent mean peak concentration (C_{max}) compared to 50 mg indomethacin IR capsules. The median time to reach peak concentrations (T_{max}) was 1.67 hours and 2.02 hours for TIVORBEX capsules and Indomethacin IR capsules, respectively.

Absorption

Similar to indomethacin IR capsules, following single oral doses of TIVORBEX capsules 20 mg or 40 mg, indomethacin is readily absorbed. TIVORBEX Capsules attained peak plasma concentrations of approximately 1.2 and 2.4 mcg/mL, respectively, at 1.67 hours. Indomethacin is virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours following dosing.

Administration of TIVORBEX Capsules 20 mg and 40 mg was associated with dose proportional pharmacokinetics.

Taking TIVORBEX with food causes a significant decrease in the rate but not the overall extent of systemic absorption of indomethacin compared to taking TIVORBEX on an empty stomach. TIVORBEX capsules results in 46% lower C_{max}, 9% lower AUC_{inf}, and 1.33 hours delayed T_{max} (1.67 hours during fasted versus 3.00 hours during fed) under the fed condition compared to the fasted condition. Based on the food effect evaluation on the indomethacin IR capsules, the effect of food on indomethacin pharmacokinetics is comparable between TIVORBEX capsules and indomethacin IR capsules.

Distribution

Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin crosses the blood-brain barrier and the placenta, and appears in breast milk.

Elimination

Metabolism

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.

Excretion

Indomethacin is eliminated via metabolism and subsequent renal and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin). The mean half-life of indomethacin from TIVORBEX capsules 40 mg is 7.6 hours and is comparable to indomethacin IR capsules 50 mg (7.2 hours).

Specific Populations

Pediatric: The pharmacokinetics of TIVORBEX has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment: The pharmacokinetics of TIVORBEX has not been investigated in patients with hepatic impairment.

Renal Impairment: The pharmacokinetics of TIVORBEX has not been investigated in patients with renal impairment [see *Warnings and Precautions (5.6)]*.

Drug Interaction Studies

Aspirin:
In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20% [*see Drug Interactions (7)]*.

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 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Diflunisal:
In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.08 times the MRHD on a mg/m^2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.06 times [mice] and 0.12 times [rats] the MRHD on a mg/m^2 basis, respectively).

Mutagenesis
Indomethacin did not have any mutagenic effect in in vitro bacterial tests and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice.

Impairment of Fertility
Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.02 times the MRHD on a mg/m^2 basis) or a two litter reproduction study in rats (0.04 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

The efficacy of TIVORBEX for the treatment of acute pain was demonstrated in two multicenter, randomized, double-blind, placebo-controlled, parallel arm studies comparing TIVORBEX 20 mg three times daily, 40 mg twice daily, 40 mg three times daily, and placebo in patients with pain following bunionectomy (Study 1 and Study 2). The two studies enrolled a total of 835 patients with a mean age of 40 years (range 18 to 68 years) a minimal pain intensity rating of at least 40 mm on a 100-mm visual analog scale (VAS) during the 9-hour period after discontinuation of the anesthetic block following bunionectomy surgery. Patients were randomized equally across the treatment groups.

The mean pain intensity measured by VAS at baseline for all treatment groups in both studies ranged from 71 to 74 mm. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as rescue medication. There was a greater use of concomitant opioid rescue medication in placebo-treated patients than in TIVORBEX-treated patients. In Study 1, 89% of patients in the TIVORBEX 20 mg three times daily group, 90% of the patients in the TIVORBEX 40 mg twice daily group, 82% in the TIVORBEX 40 mg three times daily group, and 97% of patients in the placebo group took rescue medication for pain management during the study. In Study 2, 87% of patients in the TIVORBEX 20 mg three times daily group, 76% of the patients in the TIVORBEX 40 mg twice daily group, 80% in the TIVORBEX 40 mg three times daily group, and 89% of patients in the placebo group took rescue medication for pain management during the study.

The average pain intensities over time are depicted for the treatment groups in Figure 1 for Study 1 and Figure 2 for Study 2. In both studies, TIVORBEX Capsules 20 mg three times daily, 40 mg twice daily and 40 mg three times daily, demonstrated efficacy in pain intensity reduction compared with placebo, as measured by the sum of pain intensity difference over 0 to 48 hours after the first dose.

Figure 1 Average Pain Intensity Over 48 Hours for TIVORBEX and Placebo Groups – Study 1

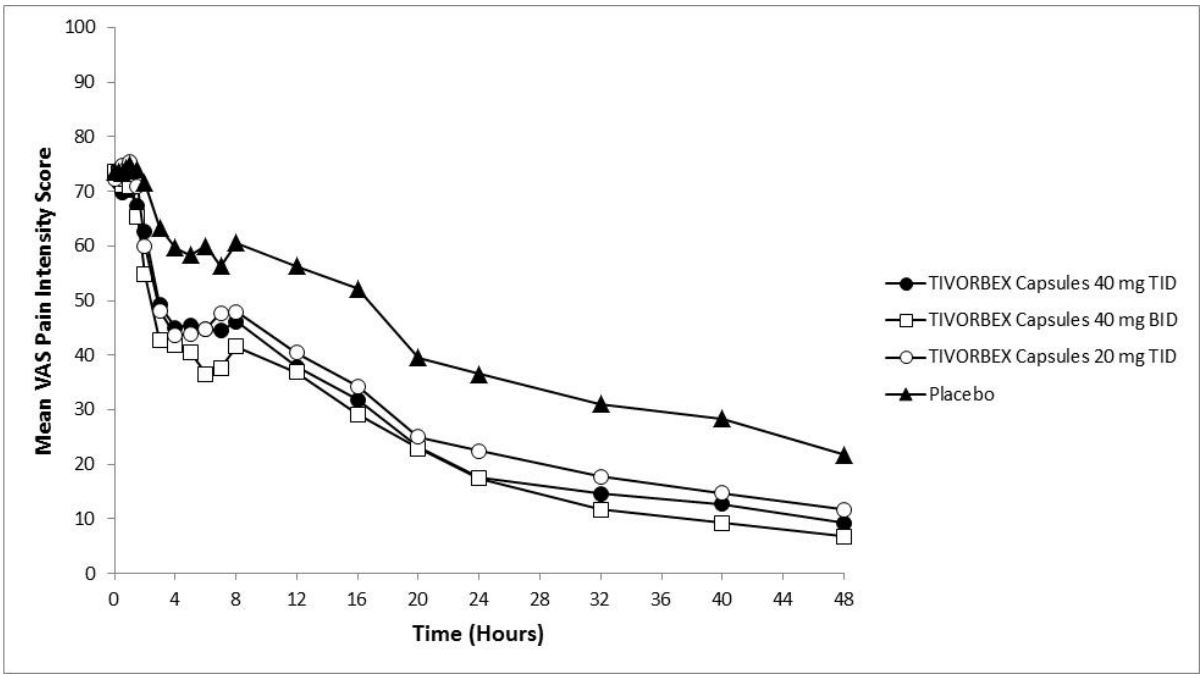
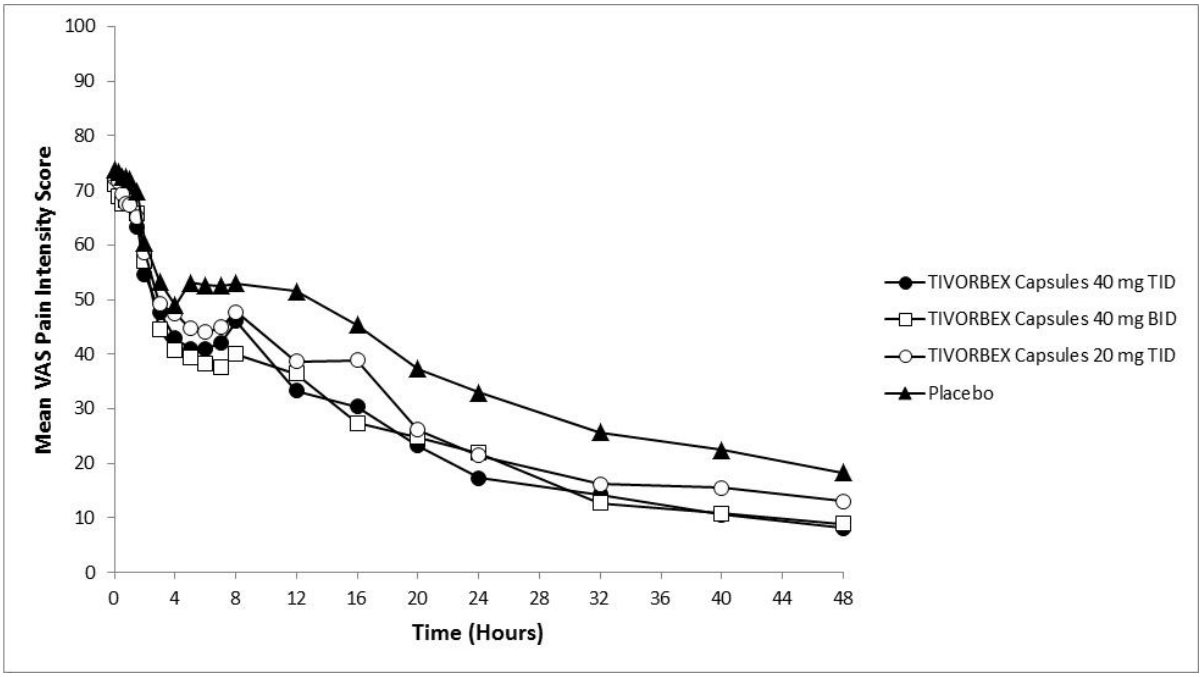


Figure 2 Average Pain Intensity Over 48 Hours for TIVORBEX and Placebo Groups – Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

TIVORBEX (indomethacin) are supplied as:

- 20 mg, dark blue body and light blue cap (imprinted IP-201 on the body and 20 mg on the cap in white ink)
  - NDC 69597-350-30, Bottles of 30 capsules
- 40 mg, dark blue body and blue cap (imprinted IP-202 on the body and 40 mg on the cap in white ink)
  - NDC 69597-349-30, Bottles of 30 capsules

Storage

Store at room temperature 20°C to 25°C (68°F to 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 and light. 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. Inform patients, families, or their caregivers of the following information before initiating therapy with TIVORBEX 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 ulcerations 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 signs and 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 TIVORBEX 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 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) and Warnings and Precautions (5.7)*].

Serious Skin Reactions, including DRESS

Advise patients to stop taking TIVORBEX immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10)*].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including TIVORBEX, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of TIVORBEX and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with TIVORBEX is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer that 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of TIVORBEX 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)* and *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 TIVORBEX until they talk to their healthcare provider [*see Drug Interactions (7)*].

Manufactured (under license from iCeutica Pty Ltd.) for:
Basiem LLC, Madisonville, LA 70447

Distributed by:
Solubiomix LLC, Madisonville, LA 70447

US Patent Nos. 8734847, 8992982, and 9089471

04/2021

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - o with increasing doses of NSAIDs
  - o with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - o anytime during use
  - o without warning symptoms
  - o that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - o increasing doses of NSAIDs
  - o longer use of NSAIDs
  - o smoking
  - o drinking alcohol
  - o older age
  - o poor health
  - o advanced liver disease
  - o bleeding problems

NSAIDs should only be used:
- o exactly as prescribed
- o at the lowest dose possible for your treatment
- o 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. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby.**You should not take NSAIDs after about 30 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.

Distributed by: Solubiomix LLC, Madisonville, LA 70447

For more information, go to WWW.SOLUBIOMIX.NET or call 1-866-511-6754.

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

Revised: 04/2021