

## 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.

#### Cardiovascular Risk

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)
- TIVORBEX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4)

#### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)

### INDICATIONS AND USAGE

TIVORBEX is a NSAID indicated for treatment of mild to moderate acute pain in adults (1).

### DOSAGE AND ADMINISTRATION

- The dosage is 20 mg orally three times daily or 40 mg orally two or three times daily. (2.1)
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.1)

### DOSAGE FORMS AND STRENGTHS

Capsules: 20 mg or 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)
- Perioperative pain in the setting of CABG surgery. (4)

### WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke can occur with NSAID treatment. Patients with known CV disease or risk factors for CV disease may be at greater risk. Use the lowest effective dose for the shortest duration possible. (5.1)
- Serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation, which can be fatal. Prescribe TIVORBEX with caution in

patients with a prior history of ulcer disease or GI bleeding. Use the lowest effective dose for the shortest duration possible. (5.2)

- Elevation of one or more liver tests and severe hepatic reactions. Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with TIVORBEX. Discontinue TIVORBEX if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.3)
- New onset or worsening of hypertension. Monitor blood pressure closely during treatment with TIVORBEX. (5.4)
- Fluid retention and edema. Prescribe TIVORBEX with caution to patients with fluid retention or heart failure. (5.5)
- Renal papillary necrosis and other renal injury with long-term use. Use TIVORBEX with caution in patients at greatest risk of renal injury, including the elderly, and patients with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and ACE inhibitors. (5.6)
- Anaphylactic reactions may occur in patients with the aspirin triad or without prior exposure to indomethacin. Seek emergency help in cases where an anaphylactic reaction occurs. (5.7)
- Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism. Use TIVORBEX, with caution in these patients. Discontinue TIVORBEX if severe CNS adverse reactions develop. (5.8)
- Serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal. Discontinue TIVORBEX if rash or other signs of local skin reaction occur. (5.9)

### ADVERSE REACTIONS

Most common adverse reactions in clinical trials (incidence  $\geq 2\%$  in TIVORBEX 20 mg and 40 mg groups) include: 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 Iroko Pharmaceuticals, LLC at 1-877-757-0676 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Co-administration with indomethacin may reduce the effect of antihypertensive agents. Concomitant use in patients with compromised renal function may result in further deterioration of renal function. (7.1, 7.3)
- Concomitant administration of indomethacin and anticoagulants and platelet inhibitors (e.g., aspirin) is not generally recommended because of the potential of increased adverse effects including increased GI bleeding. (7.2, 7.11)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on human data, indomethacin may cause fetal harm. Starting at 30 weeks gestation, TIVORBEX should be avoided as premature closure of the ductus arteriosus in the fetus may occur. (5.10, 8.1)
- Pediatric use: The safety and effectiveness of TIVORBEX in pediatric patients 17 years of age and younger has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2014

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

<b>1</b>	<b>INDICATIONS AND USAGE</b>	7.5	Diflunisal
<b>2</b>	<b>DOSAGE AND ADMINISTRATION</b>	7.6	Digoxin
2.1	Initial Dosing	7.7	Diuretics
<b>3</b>	<b>DOSAGE FORMS AND STRENGTHS</b>	7.8	Lithium
<b>4</b>	<b>CONTRAINDICATIONS</b>	7.9	Methotrexate
<b>5</b>	<b>WARNINGS AND PRECAUTIONS</b>	7.10	NSAIDs
5.1	Cardiovascular Thrombotic Events	7.11	Anticoagulants
5.2	Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation	7.12	Probenecid
5.3	Hepatic Effects	<b>8</b>	<b>USE IN SPECIFIC POPULATIONS</b>
5.4	Hypertension	8.1	Pregnancy
5.5	Congestive Heart Failure and Edema	8.3	Nursing Mothers
5.6	Renal Effects	8.4	Pediatric Use
5.7	Anaphylactic Reactions	8.5	Geriatric Use
5.8	Central Nervous System Effects	<b>10</b>	<b>OVERDOSAGE</b>
5.9	Skin Reactions	<b>11</b>	<b>DESCRIPTION</b>
5.10	Fetal Toxicity	<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>
5.11	Corticosteroid Treatment	12.1	Mechanism of Action
5.12	Masking of Inflammation and Fever	12.3	Pharmacokinetics
5.13	Hematological Effects	<b>13</b>	<b>NONCLINICAL TOXICOLOGY</b>
5.14	Use in Patients with Preexisting Asthma	13.1	Carcinogenesis, Mutagenesis, and Impairment of Fertility
5.15	Monitoring	<b>14</b>	<b>CLINICAL STUDIES</b>
5.16	Ocular Effects	<b>16</b>	<b>HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>6</b>	<b>ADVERSE REACTIONS</b>	<b>17</b>	<b>PATIENT COUNSELING INFORMATION</b>
6.1	Clinical Trials Experience	17.1	Cardiovascular Effects
6.2	Adverse Reactions From Spontaneous Reports	17.2	Gastrointestinal Effects
<b>7</b>	<b>DRUG INTERACTIONS</b>	17.3	Adverse Skin Reactions
7.1	ACE-inhibitors and Angiotensin II Antagonists	17.4	Weight Gain and Edema
7.2	Aspirin	17.5	Hepatotoxicity
7.3	Beta-adrenoceptor Blocking Agents	17.6	Anaphylactic Reactions
7.4	Cyclosporine	17.7	Fetal Toxicity

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

## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

#### Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. [see *Warnings and Precautions (5.1)*]
- TIVORBEX is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. [see *Contraindications (4)*]

#### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. [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 Initial Dosing

For treatment of mild to moderate acute pain, the dosage is 20 mg three times daily or 40 mg two or three times daily. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

## 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 patients with the following:

- 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)*]

- A history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7,5.14)*]
- Perioperative pain 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, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Inform patients about the signs and/or symptoms of serious CV events and the steps to take if they occur.

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 MI and stroke [*see Contraindications (4)*].

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, does increase the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

### **5.2 Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation**

NSAIDs, including TIVORBEX, can 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 occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term NSAID therapy is not without risk.

In patients taking indomethacin, intestinal ulceration has been associated with stenosis and obstruction. Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur.

Prescribe NSAIDs, including TIVORBEX, with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids or anticoagulants, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternative therapies that do not include NSAIDs should be considered.

### **5.3 Hepatic Effects**

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including TIVORBEX. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver test values have occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with indomethacin. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TIVORBEX immediately.

### **5.4 Hypertension**

NSAIDs, including TIVORBEX, can lead to new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events.

Use NSAIDs, including TIVORBEX, with caution in patients with hypertension. Monitor blood pressure (BP) closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides or loop diuretics or beta-adrenoceptor blocking agents may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7.1, 7.3, 7.7)*].

### **5.5 Congestive Heart Failure and Edema**

Fluid retention and edema have been observed in some patients taking NSAIDs. Use TIVORBEX with caution in patients with fluid retention or heart failure.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

## 5.6 Renal Effects

Use caution when initiating treatment with TIVORBEX in patients with considerable dehydration.

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 a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate over renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, patients with volume depletion, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state [*see Drug Interactions (7.1, 7.7)*].

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

### Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of indomethacin in patients with advanced renal disease. Therefore, treatment with TIVORBEX is not recommended in patients with advanced renal disease. If TIVORBEX therapy must be initiated, monitor patient renal function closely.

## 5.7 Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur in patients without known prior exposure to TIVORBEX. TIVORBEX is contraindicated in patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [*see Contraindications (4)*].

Seek emergency help in cases where an anaphylactic reaction occurs.

## 5.8 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.

## 5.9 Skin Reactions

NSAIDs, including TIVORBEX, 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. Patients should be informed about the signs and symptoms of serious skin manifestations, and discontinue the use of TIVORBEX at the first appearance of skin rash or any other sign of hypersensitivity [*see Contraindications (4)*].

## 5.10 Fetal Toxicity

Starting at 30 weeks gestation, TIVORBEX and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (8.1)*].

## 5.11 Corticosteroid Treatment

TIVORBEX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

## 5.12 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 infectious complications of presumed noninfectious, painful conditions.

## 5.13 Hematological Effects

Anemia may occur in patients receiving NSAIDs, including TIVORBEX. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients receiving long-term therapy with NSAIDs, including TIVORBEX, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss. TIVORBEX is not indicated for long-term treatment.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Carefully monitor patients treated with TIVORBEX who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

## 5.14 Use in Patients with Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, TIVORBEX is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma [*see Contraindications (4)*].

## 5.15 Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. For patients on long-term treatment with NSAIDs, periodically check their CBC and chemistry profile including liver function tests. Discontinue TIVORBEX if clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen. TIVORBEX is not indicated for long-term treatment.

## 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 serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Gastrointestinal effects [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Hepatic effects [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Congestive heart failure and edema [*see Warnings and Precautions (5.5)*]
- Renal effects [*see Warnings and Precautions (5.6)*]
- Anaphylactic reactions [*see Warnings and Precautions (5.7)*]
- Central nervous system effects [*see Warnings and Precautions (5.8)*]
- Skin reactions [*see Warnings and Precautions (5.9)*]

### 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 ( $\geq 2\%$  in TIVORBEX 20 mg or 40 mg group) - Phase 3 Studies in Patients With Postsurgical Pain**

Any Treatment Emergent AE	TIVORBEX	TIVORBEX	TIVORBEX	Placebo*
	40 mg three	40 mg twice	20 mg three	
	times daily*	daily*	times daily*	
	(%)	(%)	(%)	(%)
	N=187	N=184	N=183	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 Adverse Reactions From Spontaneous Reports

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 pre-existing 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).

**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, angitis, 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

### 7.1 ACE-inhibitors and Angiotensin II Antagonists

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists. Indomethacin can reduce the antihypertensive effects of captopril and losartan. These interactions should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors or angiotensin II antagonists. In some patients with compromised renal function, the co-administration of an NSAID and an ACE-inhibitor or an angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible [*see Warnings and Precautions (5.6)*].

### 7.2 Aspirin

When administered with aspirin, indomethacin's protein binding is reduced, although the clearance of free indomethacin is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of indomethacin and aspirin is not generally recommended because of the potential of increased adverse effects.

The use of indomethacin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin alone. In a clinical study of the combined use of indomethacin and aspirin, the incidence of gastrointestinal side effects was significantly increased with combined therapy.

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%.

### 7.3 Beta-adrenoceptor Blocking Agents

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by NSAIDs including indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained.

### 7.4 Cyclosporine

Administration of NSAIDs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. Use caution when NSAIDs are administered concomitantly with cyclosporine. Carefully monitor patients with impaired renal function.

### 7.5 Diflunisal

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.

## 7.6 Digoxin

Indomethacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

## 7.7 Diuretics

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

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.

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.

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

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

During concomitant therapy with NSAIDs, observe patients closely for signs of renal failure, as well as to assure diuretic efficacy [*see Warnings and Precautions (5.6)*].

## 7.8 Lithium

NSAIDs, including indomethacin, have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity. See the Prescribing Information for lithium preparations before use of such concomitant therapy. In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

## 7.9 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

## 7.10 NSAIDs

The concomitant use of indomethacin with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.

## 7.11 Anticoagulants

Caution should be exercised when NSAIDs, such as indomethacin, and anticoagulants are administered concomitantly. The effects of anticoagulants (such as warfarin) and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that with use of either drug alone.

## 7.12 Probenecid

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, 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.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

**Pregnancy Category C prior to 30 weeks gestation;**

**Category D starting at 30 weeks gestation.**

### *Risk Summary*

There are no adequate and well-controlled studies of TIVORBEX in pregnant women. Starting at 30 weeks gestation, TIVORBEX, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. TIVORBEX can cause fetal harm when administered starting at 30 weeks gestation. If the drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to the fetus. Prior to 30 weeks gestation, TIVORBEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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).

### *Clinical Considerations*

#### Fetal and Neonatal Adverse Reactions

The known effects of indomethacin and other NSAIDs on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus, tricuspid incompetence, and pulmonary hypertension; non-closure of the ductus arteriosus postnatally which may be resistant to medical management; myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis.

#### Labor or Delivery

The effects of TIVORBEX on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased pup survival.

## 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<sup>2</sup> 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<sup>2</sup> basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

Maternal indomethacin administration of 4.0 mg/kg/day 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. 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.

### **8.3 Nursing Mothers**

Based on available published data, indomethacin may be present in human milk. 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 µg/day or 4.5 µg/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. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when TIVORBEX is administered to a nursing woman.

### **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**

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older) since advancing age appears to increase the possibility of adverse reactions. Elderly patients seem to tolerate ulceration or bleeding less well than other individuals and many spontaneous reports of fatal GI events are in this population [*see Warnings and Precautions (5.2)*].

Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.2)*]; physicians should remain alert to the possibility of such adverse effects in the elderly.

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function [see *Warnings and Precautions* (5.6)].

## 10 OVERDOSAGE

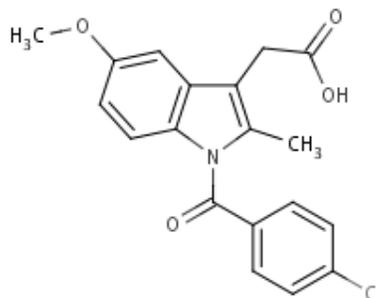
The following symptoms may be observed following overdose: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness, and convulsions.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

## 11 DESCRIPTION

TIVORBEX (indomethacin) Capsules contains the indole derivative NSAID indomethacin. TIVORBEX is 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 structural formula.



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

TIVORBEX is a NSAID with analgesic and antipyretic and analgesic 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 are reached during therapy which have been demonstrated to produce in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since 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.

### *Metabolism*

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl 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).

### *Special 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)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, and 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> basis) or a two litter reproduction study in rats (0.04 times the MRHD on a mg/m<sup>2</sup> basis).

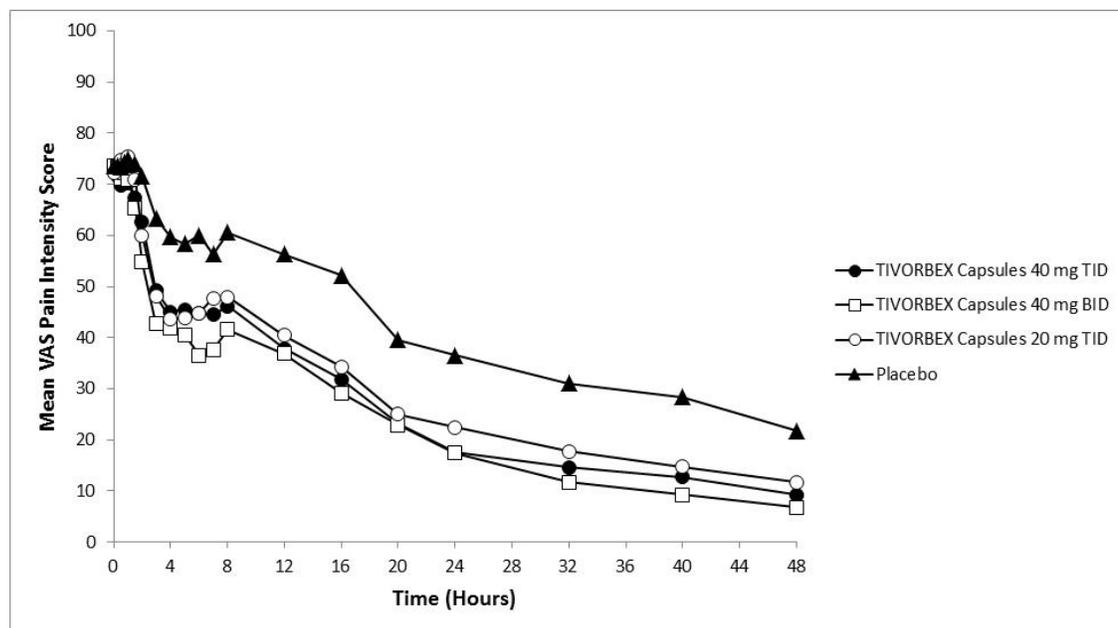
## 14 CLINICAL STUDIES

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.

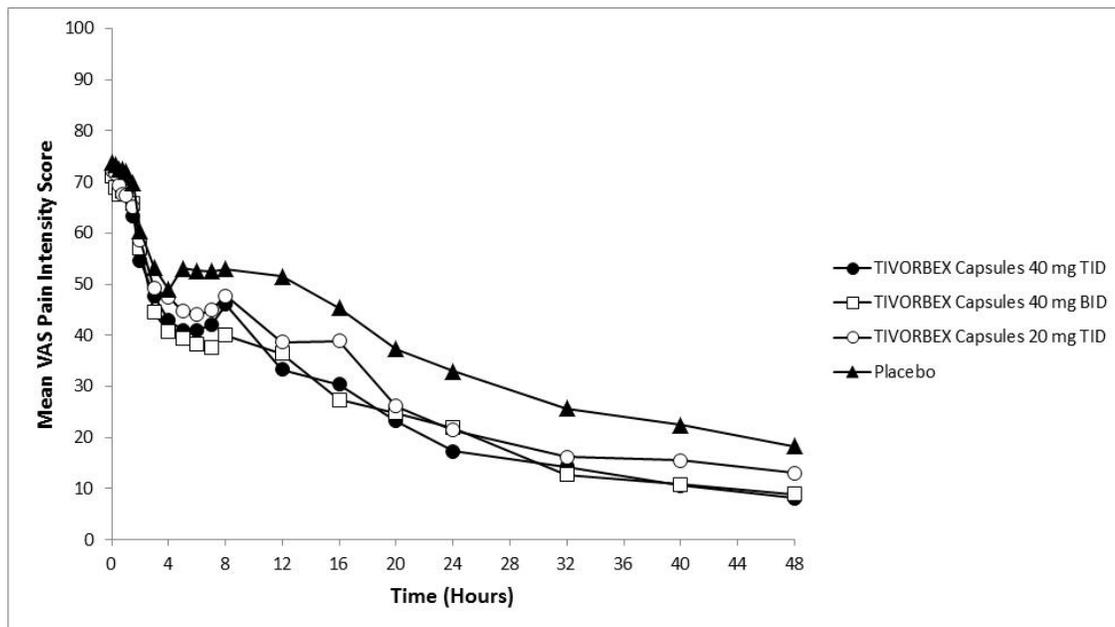
The mean pain intensity measured by VAS at baseline for all treatment groups in both studies ranged from 71 to 74 mm. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as rescue medication. There was a greater use of concomitant opioid rescue medication in placebo-treated 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, NDC (42211-201-23), Bottles of 30 capsules
- 20 mg, NDC (42211-201-29), Bottles of 90 capsules
- 40 mg, NDC (42211-202-23), Bottles of 30 capsules
- 40 mg, NDC (42211-202-29), Bottles of 90 capsules

### Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-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

See FDA-approved patient labeling ([Medication Guide](#)). Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

### 17.1 Cardiovascular Effects

NSAIDs, including TIVORBEX, may cause serious CV side effects, such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious

CV events can occur without warning symptoms, advise patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up [*see Warnings and Precautions (5.1)*].

## 17.2 Gastrointestinal Effects

NSAIDs, including TIVORBEX, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, advise patients to be alert for the signs and symptoms of ulcerations and bleeding, and to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Inform patients of the importance of this follow-up [*see Warnings and Precautions (5.2)*].

## 17.3 Adverse Skin Reactions

NSAIDs, like TIVORBEX, can cause serious skin side effects such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, advise patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible [*see Warnings and Precautions (5.9)*].

## 17.4 Weight Gain and Edema

Advise patients to promptly report to their physicians signs or symptoms of unexplained weight gain or edema during treatment with TIVORBEX [*see Warnings and Precautions (5.5)*].

## 17.5 Hepatotoxicity

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

## 17.6 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 Warnings and Precautions (5.7)*].

## 17.7 Fetal Toxicity

Inform pregnant women to avoid use of TIVORBEX and other NSAIDs starting at 30 weeks gestation, [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

This label may not be the latest approved by FDA.  
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

**Manufactured (under license from iCeutica Pty Ltd.) for and Distributed by:**  
Iroko Pharmaceuticals, LLC  
One Kew Place  
150 Rouse Boulevard  
Philadelphia, PA 19112

## **Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

---

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

**NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.** This chance increases:

- with increasing doses of NSAID medicines
- with longer use of NSAID medicines
- in people who have heart disease

**NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."**

**NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:**

- can happen without warning symptoms
- may cause death

**The chance of a person getting an ulcer or bleeding increases with:**

- increasing doses of NSAID medicines
- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

**NSAID medicines should only be used:**

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

### **What are Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines 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 a Nonsteroidal Anti-Inflammatory Drug (NSAID)?**

**Do not take an NSAID medicine:**

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

**Tell your healthcare provider:**

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant, **NSAID medicines should not be used past 30 weeks of pregnancy.**
- if you are breastfeeding, **talk to your doctor.**

**What are the possible side effects of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?**

<b>Serious side effects include:</b>	<b>Other side effects include:</b>
<ul style="list-style-type: none"><li>• heart attack</li><li>• stroke</li><li>• high blood pressure</li><li>• heart failure from body swelling (fluid retention)</li><li>• kidney problems including kidney failure</li><li>• bleeding and ulcers in the stomach and intestine</li><li>• low red blood cells (anemia)</li><li>• life-threatening skin reactions</li><li>• life-threatening allergic reactions</li><li>• liver problems including liver failure</li><li>• asthma attacks in people who have asthma</li></ul>	<ul style="list-style-type: none"><li>• stomach pain</li><li>• constipation</li><li>• diarrhea</li><li>• gas</li><li>• heartburn</li><li>• nausea</li><li>• vomiting</li><li>• dizziness</li></ul>

**Get emergency help right away if you have 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 your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:**

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- 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 and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

**Other information about Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

- Aspirin is an NSAID medicine 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 of these NSAID medicines 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.

**NSAID medicines requiring a prescription**

<b>Generic Name</b>	<b>Tradename</b>
Celecoxib	Celebrex
Diclofenac	Zorvolex, Cataflam, Cambia, Voltaren, Voltaren gel, Arthrotec (combined with misoprostol), Flector, Zipsor, Pennsaid
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, *Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone), Duexis (combined with famotidine)
Indomethacin	Tivorbex, Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail, Nexcede
Ketorolac	Toradol, Sprix
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole), Treximet (combined with sumatriptan succinate) and Vimovo (combined with esomeprazole magnesium)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

\*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

The brands listed are the trademarks or register marks of their respective owners and are not trademarks or register marks of Iroko.

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

**Manufactured (under license from iCeutica Pty Ltd) for and Distributed by:**

Iroko Pharmaceuticals, LLC  
One Kew Place  
150 Rouse Boulevard  
Philadelphia, PA 19112

Issued: February 2014