TOLMETIN SODIUM - tolmetin sodium capsule
Rising Pharma Holdings, Inc.

Tolmetin Sodium Capsules, USP
400 mg

Rx only

BOXED WARNING

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).
- Tolmetin sodium capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONS and WARNINGS).

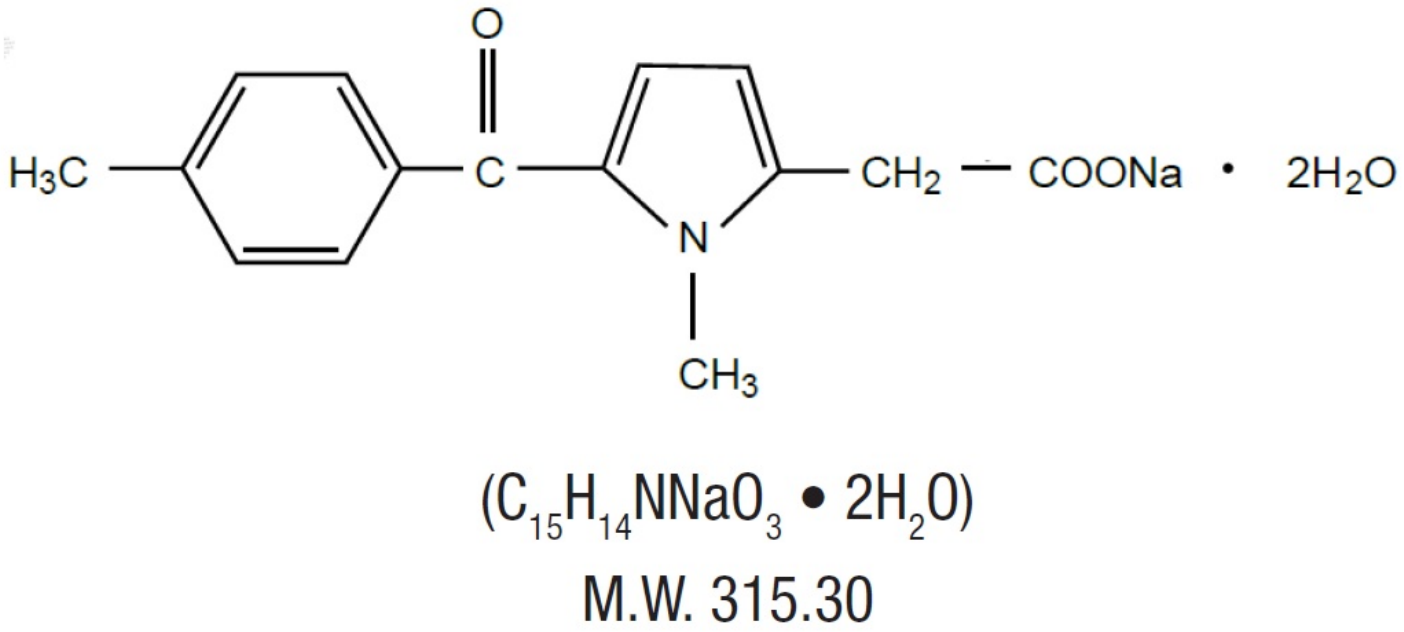
Gastrointestinal Risk

- 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).

DESCRIPTION

Each capsule for oral administration contains 492 mg of tolmetin sodium, USP as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The empty gelatin capsule shells contain FD&C Blue No. 1, gelatin, and titanium dioxide. In addition, the imprinting ink contains black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol, and shellac glaze.

The pKa of tolmetin is 3.5 and tolmetin sodium is freely soluble in water, soluble in methanol and slightly soluble in alcohol. Tolmetin sodium is a nonselective nonsteroidal anti-inflammatory agent. The structural formula is:



Sodium 1-methyl-5 *p*-toluoylpyrrole-2-acetate dihydrate.

CLINICAL PHARMACOLOGY

Studies in animals have shown tolmetin sodium to possess anti-inflammatory, analgesic, and antipyretic activity. In the rat, tolmetin prevents the development of experimentally induced polyarthritis and also decreases established inflammation.
The mode of action of tolmetin is not known. However, studies in laboratory animals and man have demonstrated that the anti-inflammatory action of tolmetin is *not* due to pituitary-adrenal stimulation. Tolmetin inhibits prostaglandin synthetase *in vitro* and lowers the plasma level of prostaglandin E in man. This reduction in prostaglandin synthesis may be responsible for the anti-inflammatory action. Tolmetin does not appear to alter the course of the underlying disease in man.

In patients with rheumatoid arthritis and in normal volunteers, tolmetin sodium is rapidly and almost completely absorbed with peak plasma levels being reached within 30 to 60 minutes after an oral therapeutic dose. In controlled studies, the time to reach peak tolmetin plasma concentration is approximately 20 minutes longer following administration of a 600 mg tablet, compared to an equivalent dose given as 200 mg tablets. The clinical meaningfulness of this finding, if any, is unknown. Tolmetin displays a biphasic elimination from the plasma consisting of a rapid phase with a half-life of 1 to 2 hours followed by a slower phase with a half-life of about 5 hours. Peak plasma levels of approximately 40 mcg/mL are obtained with a 400 mg oral dose. Essentially all of the administered dose is recovered in the urine in 24 hours either as an inactive oxidative metabolite or as conjugates of tolmetin. An 18-day multiple dose study demonstrated no accumulation of tolmetin when compared with a single dose.

In two fecal blood loss studies of 4 to 6 days duration involving 15 subjects each, tolmetin did not induce an increase in blood loss over that observed during a 4-day drug

free control period. In the same studies, aspirin produced a greater blood loss than occurred during the drug free control period, and a greater blood loss than occurred during the tolmetin sodium treatment period. In one of the two studies, indomethacin produced a greater fecal blood loss than occurred during the drug free control period; in the second study, indomethacin did not induce a significant increase in blood loss.

Tolmetin is effective in treating both the acute flares and in the long-term management of the symptoms of rheumatoid arthritis, osteoarthritis and juvenile rheumatoid arthritis.

In patients with either rheumatoid arthritis or osteoarthritis, tolmetin is as effective as aspirin and indomethacin in controlling disease activity, but the frequency of the milder gastrointestinal adverse effects and tinnitus was less than in aspirin-treated patients, and the incidence of central nervous system adverse effects was less than in indomethacin-treated patients.

In patients with juvenile rheumatoid arthritis, tolmetin is as effective as aspirin in controlling disease activity, with a similar incidence of adverse reactions. Mean SGOT values, initially elevated in patients on previous aspirin therapy, remained elevated in the aspirin group and decreased in the tolmetin sodium group.

Tolmetin has produced additional therapeutic benefit when added to a regimen of gold salts and, to a lesser extent, with corticosteroids. Tolmetin should not be used in conjunction with salicylates since greater benefit from the combination is not likely, but the potential for adverse reactions is increased.

INDICATIONS & USAGE

Carefully consider the potential benefits and risks of tolmetin sodium capsules, USP and other treatment options before deciding to use tolmetin sodium capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

Tolmetin sodium capsules are indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. Tolmetin sodium capsules are indicated in the treatment of acute flares and the long-term management of the chronic disease.

Tolmetin sodium capsules are also indicated for treatment of juvenile rheumatoid arthritis. The safety and effectiveness of tolmetin sodium capsules have not been established in pediatric patients under 2 years of age (see PRECAUTIONS: Pediatric Use and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Tolmetin sodium capsules are contraindicated in patients with known hypersensitivity to tolmetin sodium.

Tolmetin should not be given to patients who have experienced 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: Anaphylactoid Reactions and PRECAUTIONS: General: *Preexisting Asthma*).

Tolmetin is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

WARNINGS

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 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 tolmetin, increases the risk of serious gastrointestinal (GI) events (see WARNINGS).

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 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG (see CONTRAINDICATIONS).

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 4 years of follow-up.

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

Hypertension

NSAIDs, including tolmetin, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including tolmetin, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

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 tolmetin 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 PRECAUTIONS: Drug Interactions).

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

Gastrointestinal (GI) Effects-*Risk of Ulceration, Bleeding, and Perforation*

NSAIDs, including tolmetin, can cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the 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 to 6 months, and in about 2% to 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 therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with *a prior history of peptic ulcer disease and/or gastrointestinal 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 concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, 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, the lowest effective dose should be used 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, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported in patients treated with tolmetin.

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, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical trials regarding the use of tolmetin in patients with advanced renal disease. Therefore, treatment with tolmetin is not recommended in these patients with advanced renal disease. If tolmetin therapy must be initiated, close monitoring of the patient’s renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients with known prior exposure to tolmetin. Tolmetin should not be given to 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 and PRECAUTIONS: General: *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Serious Skin Reactions

NSAIDs, including tolmetin, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present

as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of tolmetin sodium at the first appearance of skin rash or any other sign of hypersensitivity. Tolmetin sodium is contraindicated in patients with previous serious skin reactions to NSAIDs (see CONTRAINDICATIONS).

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 tolmetin sodium capsules. 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 abnormalities, 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 involved. 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 tolmetin sodium capsules and evaluate the patient immediately.

Fetal Toxicity- ***Premature Closure of Fetal Ductus Arteriosus***

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

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including tolmetin sodium capsules, 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 tolmetin sodium capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if tolmetin sodium capsules treatment extends beyond 48 hours. Discontinue tolmetin sodium capsules if oligohydramnios occurs and follow up according to clinical practice (see PRECAUTIONS: Pregnancy).

PRECAUTIONS

GENERAL PRECAUTIONS

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

The pharmacological activity of tolmetin in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Opthalmological Effects: Because of ocular changes observed in animals and of reports of adverse eye findings with NSAIDs, it is recommended that patients who develop visual disturbances during treatment with tolmetin have ophthalmologic evaluations.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including tolmetin. 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 an abnormal liver test has occurred should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with tolmetin. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), tolmetin should be discontinued.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs including tolmetin. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including tolmetin, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. 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. Patients receiving tolmetin who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

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, tolmetin should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

INFORMATION FOR PATIENTS

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.

1. **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 healthcare provider immediately (see WARNINGS).
2. Tolmetin, like other NSAIDs, 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, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS: Gastrointestinal (GI) Effects: *Risk of Ulceration, Bleeding, and Perforation*).
3. **Serious Skin Reactions, including DRESS:** Advise patients to stop taking tolmetin sodium capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible (see WARNINGS).
4. **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).
5. Patients should be informed 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, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
7. **Fetal Toxicity:** Inform pregnant women to avoid use of tolmetin sodium capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with tolmetin sodium capsules 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 than 48 hours (see WARNINGS: Fetal Toxicity, PRECAUTIONS: Pregnancy).

LABORATORY TESTS

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. 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, tolmetin should be discontinued.

DRUG INTERACTIONS

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE Inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE Inhibitors.
Aspirin: As with other NSAIDs, concomitant administration of tolmetin sodium and aspirin is not generally recommended because of the potential of increased adverse effects.

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. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs 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, subjects should be observed carefully for signs of lithium toxicity.

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. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

The *in vitro* binding of warfarin to human plasma proteins is unaffected by tolmetin, and tolmetin does not alter the prothrombin time of normal volunteers. However, increased prothrombin time and bleeding have been reported in patients on concomitant tolmetin and warfarin therapy. Therefore, caution should be exercised when administering tolmetin to patients on anticoagulants.

Hypoglycemic Agents: In adult diabetic patients under treatment with either sulfonylureas or insulin there is no change in the clinical effects of either tolmetin or the hypoglycemic agents.

DRUG & OR LABORATORY TEST INTERACTIONS

Drug/Laboratory Test Interactions: The metabolites of tolmetin sodium in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g., sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g., Albustix®, Uristix®, etc.).

Drug-Food Interactions: In a controlled single-dose study, administration of tolmetin

with milk had no effect on peak plasma tolmetin concentrations, but decreased total tolmetin bioavailability by 16%. When tolmetin was taken immediately after a meal, peak plasma tolmetin concentrations were reduced by 50% while total bioavailability was again decreased by 16%.

CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY

Tolmetin sodium did not possess any carcinogenic liability in the following long-term studies: a 24-month study in rats at doses as high as 75 mg/kg/day, and an 18-month study in mice at doses as high as 50 mg/kg/day.

No mutagenic potential of tolmetin sodium was found in the Ames Salmonella-Microsomal Activation Test.

Reproductive studies revealed no impairment of fertility in animals. Effects on parturition have been shown, however, as with other prostaglandin inhibitors. This information is detailed in the Pregnancy section.

PREGNANCY

Risk Summary: Use of NSAIDs, including tolmetin sodium capsules, 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 tolmetin sodium capsules use between about 20 and 30 weeks of gestation, and avoid tolmetin sodium capsules use at about 30 weeks of gestation and later in pregnancy (see WARNINGS: Fetal Toxicity).

Premature Closure of Fetal Ductus Arteriosus: Use of NSAIDs, including tolmetin sodium capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal 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.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies in rats and rabbits at doses up to 50 mg/kg (1.5 times the maximum clinical dose based on a body weight of 60 kg) there revealed no evidence of teratogenesis or impaired fertility due to tolmetin. However, animal reproduction studies are not always predictive of human response. 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 tolmetin, 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 tolmetin sodium capsules, can cause premature closure of the fetal ductus arteriosus (see WARNINGS: Fetal Toxicity).

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 tolmetin sodium capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue tolmetin sodium capsules and follow up according to clinical practice (see WARNINGS: Fetal Toxicity).

Data: *Human Data:* There are no adequate, well controlled studies in pregnant women. Tolmetin sodium capsules should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 infrequently 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.

LABOR & DELIVERY

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

NURSING MOTHERS

Tolmetin sodium has been shown to be secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tolmetin sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

GERIATRIC USE

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS

The adverse reactions which have been observed in clinical trials encompass observations in about 4,370 patients treated with tolmetin sodium, over 800 of whom have undergone at least one year of therapy. These adverse reactions, reported below by body system, are among those typical of nonsteroidal anti-inflammatory drugs and, as expected, gastrointestinal complaints were most frequent. In clinical trials with tolmetin, about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Incidence Greater Than 1%: The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials:

Gastrointestinal: nausea (11%), dyspepsia*, gastrointestinal distress*, abdominal pain*, diarrhea*, flatulence*, vomiting*, constipation, gastritis, and peptic ulcer. Forty percent of the ulcer patients had a prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs including corticosteroids, which are known to produce peptic ulceration.

Body as a Whole: headache*, asthenia*, chest pain

Cardiovascular: elevated blood pressure*, edema*

Central Nervous System: dizziness*, drowsiness, depression

Metabolic/Nutritional: weight gain*, weight loss*

Dermatologic: skin irritation

Special Senses: tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. These are similar to changes reported with other nonsteroidal anti-inflammatory drugs.

Urogenital: elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with tolmetin sodium.

Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1%: (Causal Relationship Probable) The following adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing. The probability exists that there is a causal relationship between tolmetin and these adverse reactions.

Gastrointestinal: gastrointestinal bleeding with or without evidence of peptic ulcer, perforation, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: anaphylactoid reactions, fever, lymphadenopathy, serum sickness

Hematologic: hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: congestive heart failure in patients with marginal cardiac function

Dermatologic: urticaria, purpura, erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis, and fixed drug eruption (FDE)

Urogenital: hematuria, proteinuria, dysuria, renal failure

Incidence Less Than 1%: (Causal Relationship Unknown) Other adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing, but a causal relationship between tolmetin and the reaction could not be determined. These rarely reported reactions are being listed as alerting information for the physician since the possibility of a causal relationship cannot be excluded.

Body as a Whole: epistaxis

Special Senses: optic neuropathy, retinal and macular changes

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharma Holdings, Inc. at 1-844-874-7464 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

OVERDOSAGE

MANAGEMENT OF OVERDOSAGE: In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage followed by the administration of activated charcoal.

DOSAGE & ADMINISTRATION

Carefully consider the potential benefits and risks of tolmetin sodium capsules and other treatment options before deciding to use tolmetin sodium capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with tolmetin sodium capsules, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of rheumatoid arthritis or osteoarthritis, the recommended starting dose for adults is 400 mg three times daily (1200 mg daily), preferably including a dose on arising and a dose at bedtime. To achieve optimal therapeutic effect the dose should be adjusted according to the patient's response after 1 or 2 weeks. Control is usually achieved at doses of 600 mg to 1800 mg daily in divided doses (generally t.i.d.). Doses larger than 1800 mg/day have not been studied and are not recommended.

For the relief of juvenile rheumatoid arthritis, the recommended starting dose for pediatric patients (2 years and older) is 20 mg/kg/day in divided doses (t.i.d. or q.i.d.). When control has been achieved, the usual dose ranges from 15 to 30 mg/kg/day. Doses higher than 30 mg/kg/day have not been studied, and, therefore, are not recommended.

A therapeutic response to tolmetin sodium can be expected in a few days to a week. Progressive improvement can be anticipated during succeeding weeks of therapy. If gastrointestinal symptoms occur, tolmetin sodium capsules can be administered with antacids other than sodium bicarbonate. Tolmetin sodium bioavailability and pharmacokinetics are not significantly affected by acute or chronic administration of magnesium and aluminum hydroxides; however, bioavailability is affected by food or milk (see PRECAUTIONS: Drug-Food Interaction).

HOW SUPPLIED

Tolmetin Sodium Capsules, USP are available containing 492 mg of tolmetin sodium, USP as the dihydrate in an amount equivalent to 400 mg of tolmetin.

The 400 mg capsules are size “0”, hard-shell gelatin capsule with light blue opaque cap and light blue opaque body imprinted with “R26” on body with black ink containing off-white powder.

They are available as follows:

Bottles of 30 capsules NDC 16571-826-03
Bottles of 90 capsules NDC 16571-826-09

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Manufactured for:
Rising Pharma Holdings, Inc.
East Brunswick, NJ 08816

Revised: 12/2024

200606

PIR82601-03

PHARMACIST: Dispense a Medication Guide with each prescription.

SPL MEDGUIDE

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:
  - with increasing doses of NSAIDs
  - 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:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
- increasing doses of NSAIDs
- older age
- longer use of NSAIDs
- poor health
- smoking
- advanced liver disease
- drinking alcohol
- bleeding problems

NSAIDs should only be used:

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

What are NSAIDs?

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

Who should not take NSAIDs?
Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. 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
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- 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 they were not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. They 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.

This Medication Guide has been approved by the U.S. Food and Drug Administration. The brands listed are trademarks of their respective owners.

Manufactured for:
Rising Pharma Holdings, Inc.
East Brunswick, NJ 08816

Issued: 02/2023

200606

MGR82601-00

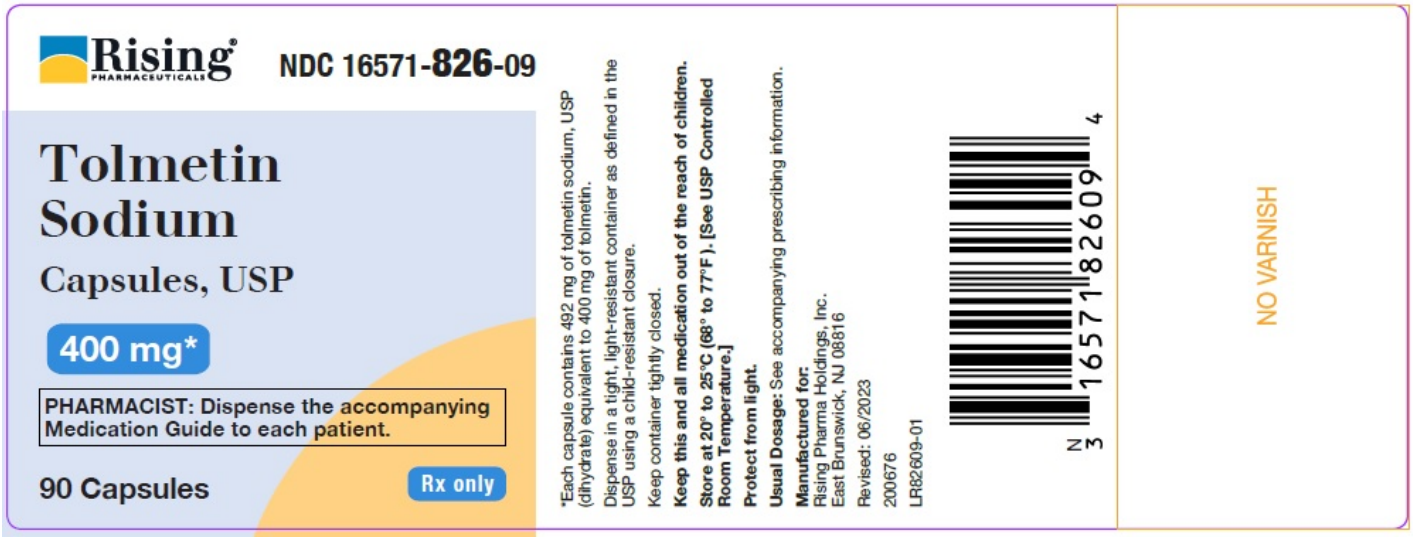
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Rising Pharma Holdings, Inc. NDC 16571-826-09

Tolmetin Sodium Capsules, USP

400 mg (90 Capsules Bottle)

Rx only



TOLMETIN SODIUM

tolmetin sodium capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16571-826
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TOLMETIN SODIUM (UNII: 02N1TZF99F) (TOLMETIN - UNII:D8K2JPN18B)	TOLMETIN	400 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	
FD&C BLUE NO. 1 ALUMINUM LAKE (UNII: J9EQA3S2JM)	
FD&C BLUE NO. 2 ALUMINUM LAKE (UNII: 4AQJ3LG584)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
MICROCRYSTALLINE CELLULOSE 102 (UNII: PNR0YF693Y)	

Product Characteristics			
Color	BLUE (light blue opaque cap and light blue opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	R26
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16571-826-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2023	05/31/2026

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA073393	06/30/2023	05/31/2026

Labeler - Rising Pharma Holdings, Inc. (116880195)

Establishment

Name	Address	ID/FEI	Business Operations
APPCO PHARMA LLC		078510186	ANALYSIS(16571-826) , MANUFACTURE(16571-826) , PACK(16571-826)

Revised: 12/2024 Rising Pharma Holdings, Inc.