TOLMETIN SODIUM- tolmetin sodium capsule
TOLMETIN SODIUM- tolmetin sodium tablet
Mutual Pharmaceutical Company, Inc.

TOLMETIN SODIUM CAPSULES USP
TOLMETIN SODIUM TABLETS USP

Rx only

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**).
- Tolmetin sodium is contraindicated for the treatment of peri-operative pain 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 anytime during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See **WARNINGS**).

DESCRIPTION

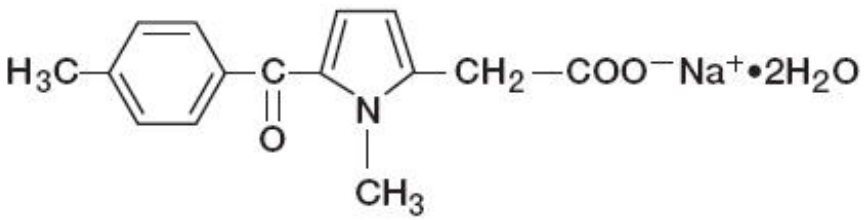
Each tolmetin sodium capsule, for oral administration, contains 492 mg of tolmetin sodium (as the dihydrate), equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium and the following inactive ingredients: FD&C Red No. 3, FD&C Yellow No. 6, gelatin, magnesium stearate, pregelatinized starch, talc and titanium dioxide.

Each tolmetin sodium tablet, for oral administration, contains 246 mg of tolmetin sodium (as the dihydrate), equivalent to 200 mg of tolmetin (scored for 100 mg). Each tablet contains 18 mg (0.784 mEq) of sodium and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate and talc.

The pKa of tolmetin is 3.5 and tolmetin sodium is freely soluble in water.

Tolmetin sodium is a nonselective nonsteroidal anti-inflammatory agent.

The structural formula is:



Sodium 1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrole-2-acetate dihydrate.

CLINICAL PHARMACOLOGY

Studies in animals have shown tolmetin sodium to possess anti-inflammatory, analgesic, and antipyretic activity. In the rat, tolmetin sodium prevents the development of experimentally induced polyarthritis and also decreases established inflammation.

The mode of action for tolmetin sodium is not known. However, studies in laboratory animals and man have demonstrated that the anti-inflammatory action of tolmetin sodium is *not* due to pituitary-adrenal stimulation. Tolmetin sodium 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 sodium 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 30–60 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 µg/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 sodium 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 sodium 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 sodium 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 sodium 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 sodium has produced additional therapeutic benefit when added to a regimen of gold salts and, to a lesser extent, with corticosteroids. Tolmetin sodium 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 AND USAGE

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

Tolmetin sodium is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. Tolmetin sodium is indicated in the treatment of acute flares and the long-term

management of the chronic disease.

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

CONTRAINDICATIONS

Tolmetin sodium is contraindicated in patients with known hypersensitivity to tolmetin sodium.

Tolmetin sodium 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: Preexisting Asthma**).

Tolmetin sodium is contraindicated for the treatment of peri-operative pain 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 three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, 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, the lowest effective dose should be used 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. Patients should be informed about the signs and/or 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 does increase the risk of serious GI events (see **WARNINGS: Gastrointestinal (GI) Effects–Risk of Ulceration, Bleeding, and Perforation**).

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 (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including tolmetin sodium, 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 sodium, 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.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Tolmetin sodium should be used with caution in patients with fluid retention or heart failure.

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

NSAIDs, including tolmetin sodium, 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 nephritic syndrome have been reported in patients treated with tolmetin sodium. 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 studies regarding the use of tolmetin sodium in patients with advanced renal disease. Therefore, treatment with tolmetin sodium is not recommended in these patients with advanced renal disease. If tolmetin sodium 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 sodium. Tolmetin sodium 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: Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including tolmetin sodium, can cause serious skin adverse events 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 use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, tolmetin sodium should be avoided because it may cause premature closure of the ductus arteriosus (see also **PRECAUTIONS: Pregnancy**).

PRECAUTIONS

General

Tolmetin sodium 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 sodium in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Ophthalmological 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 sodium 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 sodium. 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 sodium. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), tolmetin sodium should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including tolmetin sodium. 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 sodium, 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 sodium 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 sodium 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. Tolmetin sodium, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS: Cardiovascular Effects**).
2. Tolmetin sodium, 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. Tolmetin sodium, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity, such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
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. In late pregnancy, as with other NSAIDs, tolmetin sodium should be avoided because it will cause premature closure of the ductus arteriosus.

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 sodium 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 sodium and warfarin therapy. Therefore, caution should be exercised when administering tolmetin sodium 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 sodium or the hypoglycemic agents.

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 sodium with milk had no effect on peak plasma tolmetin concentrations, but decreased total tolmetin bioavailability by 16%. When tolmetin sodium 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

Teratogenic Effects: Pregnancy Category C

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) revealed no evidence of teratogenesis or impaired fertility due to tolmetin sodium. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Tolmetin sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and 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 sodium 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 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 4370 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 sodium, 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,[1] gastrointestinal distress,[1] abdominal pain,[1] diarrhea,[1]

flatulence,[1] vomiting,[1] 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,[1] asthenia,[1] chest pain

Cardiovascular: Elevated blood pressure,[1] edema[1]

Central Nervous System: Dizziness,[1] drowsiness, depression

Metabolic/Nutritional: Weight gain,[1] weight loss[1]

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

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[1] 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 controlled clinical trials or were reported since marketing. The probability exists that there is a causal relationship between tolmetin sodium 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, toxic epidermal necrolysis

Urogenital: Hematuria, proteinuria, dysuria, renal failure

Incidence Less Than 1%

(Causal Relationship Unknown)

Other adverse reactions were reported less frequently than 1 in 100 controlled clinical trials or were reported since marketing, but a causal relationship between tolmetin sodium 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

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 AND ADMINISTRATION

Carefully consider the potential benefits and risks of tolmetin sodium and other treatment options before deciding to use tolmetin sodium. 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, 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 one or two weeks. Control is usually achieved at doses of 600–1800 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 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 and tablets are supplied as follows:

Tolmetin sodium capsules equivalent to 400 mg tolmetin, orange/orange imprinted: Mutual 179

Bottles of 100	NDC 53489-507-01
Bottles of 250	NDC 53489-507-03
Bottles of 500	NDC 53489-507-05
Bottles of 1000	NDC 53489-507-10

Tolmetin sodium tablets equivalent to 200 mg tolmetin, off white, round scored, debossed: MP 50

Bottles of 50	NDC 53489-506-02
Bottles of 90	NDC 53489-506-90
Bottles of 100	NDC 53489-506-01
Bottles of 250	NDC 53489-506-03
Bottles of 500	NDC 53489-506-05
Bottles of 1000	NDC 53489-506-10

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room Temperature]

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

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Cranbury, NJ 08512

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Medication Guide for Non-Steroidal 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 Non-Steroidal 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 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:
- 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 Non-Steroidal 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 Non-Steroidal 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 by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

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
- skin rash or blisters with fever
- unusual weight gain
- 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 Non-Steroidal 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 health care provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
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.

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

Distributed by: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

Rev 03, November 2014

PRINCIPAL DISPLAY PANEL - 200 mg Tablet Bottle Label

NDC 53489-506-01

Tolmetin Sodium
Tablets USP

200 mg*

PHARMACIST: PLEASE DISPENSE
WITH MEDICATION GUIDE

Rx Only

100 Tablets

SUN
PHARMA

PRINCIPAL DISPLAY PANEL - 400 mg Capsule Bottle Label

NDC 53489-507-01

Tolmetin Sodium
Capsules USP

400 mg*

PHARMACIST: PLEASE DISPENSE
WITH MEDICATION GUIDE

Rx Only
100 Capsules

SUN
PHARMA

TOLMETIN SODIUM

tolmetin sodium capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:53489-507
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
FD&C Red No. 3 (UNII: PN2ZH5LOQY)	
FD&C Yellow No. 6 (UNII: H77VEI93A8)	
gelatin (UNII: 2G86QN327L)	
magnesium stearate (UNII: 70097M6I30)	
starch, corn (UNII: O8232NY3SJ)	
talc (UNII: 7SEV7J4R1U)	
titanium dioxide (UNII: 15FIX9V2JP)	

Product Characteristics

Color	ORANGE	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	Mutual;179
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53489-507-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:53489-507-03	250 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
3	NDC:53489-507-05	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
4	NDC:53489-507-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA073311	09/04/2009	

TOLMETIN SODIUM

tolmetin sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:53489-506
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
tolmetin sodium (UNII: 02N1TZF99F) (tolmetin - UNII:D8K2JPN18B)	tolmetin	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
cellulose, microcrystalline (UNII: OP1R32D61U)	
magnesium stearate (UNII: 70097M6I30)	
starch, corn (UNII: O8232NY3SJ)	
sodium starch glycolate type A potato (UNII: 5856J3G2A2)	
talc (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	WHITE (off white)	**Score**	2 pieces
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	MP;50
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:53489-506-02	50 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:53489-506-90	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
3	NDC:53489-506-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
4	NDC:53489-506-03	250 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
5	NDC:53489-506-05	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
6	NDC:53489-506-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA073311	09/04/2009	

Labeler - Mutual Pharmaceutical Company, Inc. (121735955)

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