

TRADENAME (Established name which should always include dosage form) Strength

DESCRIPTION

TRADENAME [established name] is a member of the ?????????? group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each [color description] tablet/capsule contains [common name] for oral administration. [Common name is a racemic mixture of [+] S- and [-] R-enantiomers.] It is a [description of the chemical substance in accordance with the USP, BP or Merck Index].

The chemical name is ??????????. The molecular weight is ??????. Its molecular formula is ??? and it has the following structural formula:

[structure]

The inactive ingredients in TRADENAME include: (list of inactive ingredients).

CLINICAL PHARMACOLOGY

Pharmacodynamics

TRADENAME is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of TRADENAME, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Absorption

TRADENAME is ??% absorbed after oral administration [as compared to IV; as compared to solution; or as measured by urinary recovery] (see Table 1). [TRADENAME's low bioavailability is due to ?????]. Food (has a, has no) significant effect on {the rate (and) the extent} of TRADENAME absorption. [(The {extent {and} rate} of TRADENAME absorption is (decreased, increased) ??% when given with food.) There is no significant food effect if the drug is given at least hours (before, after) meals.)] {The antacids A,B,C (and) Drugs X,Y,Z} have also been shown (to, not to) significantly (increase, decrease) the {extent (and) rate} of TRADENAME absorption [and concomitant use with TRADENAME is contraindicated.]

TABLE 1.

PK Parameters	Normal Healthy Adults (Age Range) [N =]	Important Special Population(s) (Gender, Age, Ethnic group, Disease) [N=]
Absolute Bioavailability (if known)	Mean (C.V.). and 95% C. I.	Separate-Column for each important population
Tmax		
Oral Clearance (CL/F)		
Renal Clearance		
Apparent Volume of Distribution (V/F, Vss/F)		

{Effective, Terminal, Distribution} Half-life	Separate Row for each	
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Distribution

The apparent volume of distribution (V_{ss}/F) of DRUG SUBSTANCE is approximately ??? L/kg. DRUG SUBSTANCE is ?? - ?? % bound to plasma proteins, primarily to {albumin, glycoproteins, lipoproteins, etc.}. Plasma protein binding (is constant, increases, decreases) over the concentration range (?? - ?? $\mu\text{g/mL}$) achieved with recommended doses [resulting in increasing free/total ratios with increasing total drug concentration]. [DRUG SUBSTANCE penetrates into red blood cells with a blood/plasma ratio = ?.?] [DRUG SUBSTANCE penetrates the {blood-brain, placental} barrier(s) to ? % (see **PRECAUTIONS**).] DRUG SUBSTANCE (is, is not) [expected to be] excreted in human milk [based on its physical-chemical properties]. [The nursing infant dose would be approximately ? mg/day.]

Metabolism

?? (number) DRUG SUBSTANCE metabolites have been identified in human plasma and urine. [Several metabolites remain to be identified]. The metabolites include W, X, Y and Z. On chronic dosing, metabolite(s) {W, X, Y, Z} (accumulate, do not accumulate) in the plasma of patients with normal renal function. Increased plasma levels of metabolite(s) {W,X,Y,Z} are observed in patients with renal dysfunction. [Concentrations of metabolite(s) X and Y are approximately ? % of the parent compound at steady-state.] Studies utilizing human liver (microsomes, slices) have demonstrated that cytochrome P₄₅₀ plays an important role in DRUG SUBSTANCE metabolism. These *in vitro* findings are consistent with the clinical observation that DRUG SUBSTANCE metabolism is (increased, reduced) in (smokers, subjects receiving DRUG Q). [Metabolites X and Y undergo further (glucuronidation, sulfation) followed by biliary excretion, enterohepatic circulation and partial elimination in the feces.]

DRUG SUBSTANCE's metabolites (have, do not have) significant pharmacologic activity. [The major metabolite, W, has been evaluated along with DRUG SUBSTANCE in receptor binding studies and *in vivo* animal models and has a demonstrated (activity, potency) of approximately ? % of the parent drug.] [A statement of the rationale for the potency estimate should be included, if available.]

Excretion

Approximately ? % of a TRADENAME dose is excreted unchanged in the urine, with ? % of the dose excreted into the urine as parent drug plus metabolites. Because renal elimination (is, is not) a significant pathway of elimination, dosing adjustment in patients with mild to moderate renal dysfunction (is, is not) necessary. The half-life ($t_{1/2}$) is ?. In patients with severe renal dysfunction or undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), dosing (must, does not need to) be modified. [Since DRUG SUBSTANCE is actively secreted in the urine via the (acid, base) pathway, concomitant use of other drugs which are substrates such as (????) for this pathway may result in a decrease in DRUG SUBSTANCE renal clearance and subsequent increase in plasma levels].

Special Populations**Pediatric**

TRADENAME (has, has not) been investigated in pediatric patients ?? yrs of age. [Clearance, $t_{1/2}$, {is, is not, are, are not} (different, decreased, increased) approximately ? % as compared to the adult population.]

Race

Pharmacokinetics differences due to race (have, have not been) identified. [Because the slow metabolize isozyme of Cytochrome P₄₅₀ is more prevalent in {Asians, Afro-Americans, Hispanics, Eskimos, American Indians, etc.}, (lower, higher) doses should be used in initiating TRADENAME therapy within (this, these) racial group(s).]

Hepatic Insufficiency

Hepatic metabolism accounts for ? % of TRADENAME elimination, so patients with {acute (and) chronic} hepatic disease (may, do not) require reduced doses of TRADENAME compared to patients with normal hepatic function. [DRUG SUBSTANCE plasma protein binding may decrease in liver disease due to reduced serum albumin (< ? mg%).]

Renal Insufficiency

TRADENAME pharmacokinetics (has, has not) been investigated in subjects with renal insufficiency. DRUG SUBSTANCE renal clearance decreased proportionally with creatinine clearance (CrCl), [but since only ? % of DRUG SUBSTANCE is excreted unchanged in the urine, the decrease in total body clearance becomes clinically important in those subjects with CrCl < ? mL/min]. DRUG SUBSTANCE (is, is not) significantly removed from the blood in patients undergoing {hemodialysis, CAPD}. DRUG SUBSTANCE plasma protein binding may decrease in patients with severe renal deficiency.]

CLINICAL STUDIES

INDICATIONS AND USAGE

TRADENAME is indicated:

- {
 - For reduction of fever [in patients age ??].
 - For relief of mild to moderate pain [in patients age ??].
 - For relief of signs and symptoms of juvenile arthritis.
 - For relief of the signs and symptoms of rheumatoid arthritis.
 - For relief of the signs and symptoms of osteoarthritis.
 - For treatment of primary dysmenorrhea.
 - For acute or long-term use in the relief of signs and symptoms of the following:
 1. Ankylosing spondylitis
 2. Acute painful shoulder (Acute subacromial bursitis/supraspinatus tendinitis)
 3. Acute gouty arthritis}

Put in the product specific indication(s)}

CONTRAINDICATIONS

TRADENAME is contraindicated in patients with known hypersensitivity to GENERIC NAME. TRADENAME 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).

WARNINGS

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

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to 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 thus, 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. 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, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to TRADENAME. TRADENAME 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.

Advanced Renal Disease

In cases with advanced kidney disease, treatment with TRADENAME is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see **PRECAUTIONS - Renal Effects**).

Pregnancy

In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

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

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including TRADENAME. 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 TRADENAME. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), TRADENAME should be discontinued.

Renal Effects

Caution should be used when initiating treatment with TRADENAME in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with TRADENAME. Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS - Advanced Renal Disease**).

As with other NSAIDs, long-term administration of TRADENAME has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which 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-dependant 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 nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

[TRADENAME metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.]

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including TRADENAME. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including TRADENAME, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

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. TRADENAME does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving TRADENAME who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore as with other NSAIDs, TRADENAME should be used with caution in patients with fluid retention, hypertension, or heart failure.

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 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, TRADENAME 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

TRADENAME, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. 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 sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Risk of Gastrointestinal Ulceration, Bleeding and Perforation**).

Patient should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

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.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see **WARNINGS**).

In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

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, TRADENAME should be discontinued.

Drug Interactions

Aspirin

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

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.

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.

Furosemide

Clinical studies, as well as post marketing observations, have shown that TRADENAME 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 (see **PRECAUTIONS, Renal Effects**), 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.

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.

Drug/Laboratory Test Interactions

Only if positive interactions have been observed. [See 201.57(f)(4)(ii)]

Carcinogenesis, Mutagenesis, Impairment of Fertility

Usually only if significant findings have been observed.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs 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 TRADENAME on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TRADENAME, 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 ??? [have, have not] been established.

Geriatric Use

Proposed NSAID Package Insert Labeling Template (Revised 12/19/96)

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

ADVERSE REACTIONS

In patients taking TRADENAME or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1 -10% of patients are:

gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting;
abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus

Additional adverse experiences reported occasionally include:

Body as a whole -	fever, infection, sepsis;
Cardiovascular system -	congestive heart failure, hypertension, tachycardia, syncope;
Digestive system -	dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleedings;
Hemic and lymphatic system -	ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia;
Metabolic and nutritional -	weight changes;
Nervous system -	anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness;
Respiratory system -	asthma, dyspnea;
Skin and appendages -	alopecia, photosensitivity, pruritus, sweat;
Special senses -	blurred vision;
Urogenital system -	cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria;

Other adverse reactions, which occur rarely are:

Body as a whole -	anaphylactic reactions, appetite changes, death;
Cardiovascular system -	arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis;
Digestive system -	eructation, liver failure, pancreatitis;
Hemic and lymphatic system -	agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia;
Metabolic and nutritional -	hyperglycemia;
Nervous system -	convulsions, coma, hallucinations, meningitis;
Respiratory -	respiratory depression, pneumonia;
Skin and appendages -	angioedema, toxic epidermal necrosis, erythema multiforma, exfoliative dermatitis;
Special senses -	conjunctivitis, hearing impairment.

OVERDOSAGE

Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAIDs 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

Proposed NSAID Package Insert Labeling Template (Revised 12/19/96)

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.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy with TRADENAME, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of ????, the recommended dose is ??? mg given orally ?? times per day.

[Different dose strengths and formulations [i.e., capsules, tablets, suspensions] of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing {formulation (type, strength)}.]

HOW SUPPLIED

(For each potency, the following in tabular format as follows:)

Dosage, description (e.g., shape, color, scoring, etc.)	
Size 1	NDC #
Size 2	NDC #
Size 3	NDC #

(Special handling and storage conditions)

Caution: Federal law prohibits dispensing without prescription.

The date, identified as such, of the most recent revision of the labeling.

Name and place of business of the manufacturer, packer, and/or distributor as required.

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