Wyeth®

Lodine®

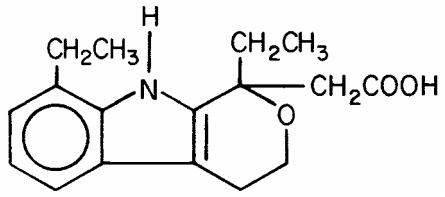
(etodolac capsules 200 and 300 mg, and etodolac tablets 400 and 500 mg)

] only

~~Description~~DESCRIPTION

Lodine® (etodolac ~~capsules and tablets~~) is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet and capsule contains etodolac for oral administration. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol. ~~chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is shown below:~~

The chemical name is (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. The molecular formula for etodolac is $C_{17}H_{21}NO_3$, and it has the following structural formula:



~~The empirical formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.~~

~~*Inactive ingredients are:*~~

The inactive ingredients in Lodine include:

—*in capsules:* cellulose, gelatin, iron oxides, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

—*in tablets:* cellulose, ~~hydroxypropyl methylcellulose~~hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide. The 400 mg tablets contain D&C Yellow #10, FD&C Blue #2, and FD&C Yellow #6 as color additives. The 500 mg tablets contain FD&C Blue #2 only.

~~Lodine is available in 200 and 300 mg capsules, and 400 and 500 mg tablets, for oral administration.~~

~~Clinical Pharmacology~~CLINICAL PHARMACOLOGY

~~PHARMACOLOGY~~Pharmacodynamics

~~Etodolac~~Lodine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of ~~etodolac~~Lodine, like that of other NSAIDs, is not ~~known~~completely understood, but ~~is believed to be associated with the inhibition of~~may be related to prostaglandin ~~biosynthesis~~synthetase inhibition.

Lodine is a racemic mixture of [-]R- and [+]S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]S-form is biologically active. Both enantiomers are stable and there is no [-]R to [+]S conversion *in vivo*.

~~PHARMACODYNAMICS~~

~~Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg Lodine, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see **Clinical Trials**).~~

~~PHARMACOKINETICS~~Pharmacokinetics

~~The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.~~

~~Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.~~

~~Lodine has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.~~

~~ABSORPTION~~*Absorption*

The systemic bioavailability of etodolac from Lodine is 100% as compared to solution and at least 80% as determined from mass balance studies. Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation~~,~~ is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations (C_{max}) range from approximately 14 ± 4 to 37 ± 9 μg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on ~~AUC (~~the area under the plasma concentration-time curve~~)~~ (AUC) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses. The extent of absorption of etodolac is not affected when Lodine is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one-half and increases the time to peak concentration by 1.4 to 3.8 hours.

Table 1. Etodolac Steady-State Pharmacokinetic Parameters
(N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability) [F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2, \alpha}$]	0.71 ± 0.50 h
Terminal half-life [$t_{1/2, \beta}$]	7.3 ± 4.0 h

Antacid Effects

The extent of absorption of etodolac is not affected when Lodine is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects

The extent of absorption of etodolac is not affected when Lodine is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Table 1. Mean (CV%)† Pharmacokinetic Parameters of Lodine in Normal Healthy Adults and Various Special Populations[1]

PK Parameters	Normal Healthy Adults (18-65)* (n=179)	Healthy Males (18-65) (n=176)	Healthy Females (27-65) (n=3)	Elderly (>65) (70-84)	Hemodialysis (24-65) (n=9) Dialysis On	Hemodialysis (24-65) (n=9) Dialysis Off	Renal Impairment (46-73) (n=10)	Hepatic Impairment (34-60) (n=9)
T_{max}h	1.4 (61%)†	1.4 (60%)	1.7 (60%)	1.2 (43%)	1.7 (88%)	0.9 (67%)	2.1 (46%)	1.1 (15%)
Oral Clearance, mL/h/kg (CL/F)	49.1 (33%)	49.4 (33%)	35.7 (28%)	45.7 (27%)	NA	NA	58.3 (19%)	42.0 (43%)
Apparent Volume of Distribution, mL/kg (Vd/F)	393 (29%)	394 (29%)	300 (8%)	414 (38%)	NA	NA	NA	NA
Terminal Half-Life, h	6.4 (22%)	6.4 (22%)	7.9 (35%)	6.5 (24%)	5.1 (22%)	7.5 (34%)	NA	5.7 (24%)

†% Coefficient of variation
*Age Range (years)
NA = not available

~~Distribution~~***Distribution***

~~Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.~~ The mean apparent volume of distribution (Vd/F) of etodolac is approximately 390 mL/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied. It is not known whether etodolac is excreted in human milk; however, based on its physical-chemical properties, excretion into breast milk is expected. Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

~~Metabolism~~***Metabolism***

Etodolac is extensively metabolized in the liver.~~, with renal elimination of etodolac and its metabolites being the primary route of excretion. The intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.~~ The role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. Several etodolac metabolites have been identified in human plasma and urine. Other metabolites remain to be identified. The metabolites include 6-, 7-, and 8-hydroxylated-etodolac and etodolac glucuronide. After a single dose of 14C-etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylated-etodolac metabolite does not accumulate in the plasma of patients with normal renal function. The extent of accumulation of hydroxylated-etodolac metabolites in patients with renal dysfunction has not been studied. The hydroxylated-etodolac metabolites undergo further glucuronidation followed by renal excretion and partial elimination in the feces.

~~Protein Binding~~
~~Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.~~

~~Elimination~~***Excretion***
The mean ~~plasma~~oral clearance of etodolac~~,~~ following oral dosing is ~~47~~49 (± 16) mL/h/kg~~.~~, ~~and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose~~Approximately 1% of a Lodine dose is excreted unchanged in the urine with 72% of the dose excreted into urine as parent drug plus metabolite:

— etodolac, unchanged	1%
— etodolac glucuronide	13%
— hydroxylated metabolites (6-, 7-, and 8-OH)	5%
— hydroxylated metabolite glucuronides	20%
— unidentified metabolites	33%

Although renal elimination is a significant pathway of excretion for etodolac metabolites, no dosing adjustment in patients with mild to moderate renal dysfunction is generally necessary. The terminal half-life ($t_{1/2}$) of etodolac is 6.4 hours (22% CV). In patients with severe renal dysfunction or undergoing hemodialysis, dosing adjustment is not generally necessary.

Fecal excretion accounted for 16% of the dose.

~~SPECIAL POPULATIONS~~**Special Populations**
~~*Elderly Patients*~~***Geriatric***
In Lodine clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic studies,~~etodolac clearance was reduced by about 15% in older patients (>65 years of age). In these studies,~~ age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. Therefore, ~~N~~no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see **PRECAUTIONS, Geriatric Use**). ~~The elderly may need dosage adjustment, however, on the basis of body size (see **Precautions** – GERIATRIC POPULATION), as they may be more sensitive to antiprostaglandin effects than younger patients (see **Precautions** – GERIATRIC POPULATION).~~

~~(b)(4)~~ (b)(4)

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **PRECAUTIONS, General, *Renal Effects***).

~~*Renal Impairment*~~
~~Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.~~

Pediatric
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Race
Pharmacokinetic differences due to race have not been identified. Clinical studies included patients of many races, all of whom responded in a similar fashion.

Hepatic ~~Impairment~~Insufficiency
Etodolac is predominantly metabolized by the liver. In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Patients with acute and chronic hepatic diseases do not generally require reduced doses of etodolac compared to patients with normal hepatic function. However, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure. Etodolac plasma protein binding did not change in patients with compensated hepatic cirrhosis given Lodine.~~Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.~~

Renal Insufficiency
Lodine pharmacokinetics have been investigated in subjects with renal insufficiency. Etodolac renal clearance was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance 37 to 88 mL/min). Furthermore, there were no significant differences in the disposition of total and free etodolac in these patients. However, etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

~~Clinical Trials~~CLINICAL STUDIES

~~ANALGESIA~~Analgesia
Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for Lodine established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Lodine 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Lodine 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of Lodine and 5 to 6 hours for 400 mg of Lodine as measured by when approximately half of the patients required remedication.

~~OSTEOARTHRITIS~~**~~Osteoarthritis~~**
The use of Lodine in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, Lodine, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

~~RHEUMATOID ARTHRITIS~~**~~Rheumatoid Arthritis~~**
In a 3-month study with 426 patients, Lodine 300 mg b.i.d. was effective in management of rheumatoid arthritis and comparable in efficacy to piroxicam 20 mg/day. In a long-term study with 1,446 patients in which 60% of patients completed 6 months of therapy and 20% completed 3 years of therapy, Lodine in a dose of 500 mg b.i.d. provided efficacy comparable to that obtained with ibuprofen 600 mg q.i.d. In clinical trials of rheumatoid arthritis patients, Lodine has been used in combination with gold, d-penicillamine, chloroquine, corticosteroids, and methotrexate.

~~Indications and Usage~~INDICATIONS AND USAGE

Lodine (etodolac capsules and tablets) is indicated: ~~for~~

- For acute and long-term use in the management of signs and symptoms of the following:
  1. ~~o~~Osteoarthritis ~~and~~
  2. ~~r~~Rheumatoid arthritis~~.~~
- ~~Lodine is also indicated f~~For the management of acute pain~~.~~

~~Contraindications~~CONTRAINDICATIONS

Lodine is contraindicated in patients with known hypersensitivity to etodolac. Lodine should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs ~~Lodine~~ have been reported in such patients (see **~~Warnings~~ WARNINGS**, **Anaphylactoid Reactions** ~~Anaphylactoid Reactions~~ and **PRECAUTIONS, General,** ***Pre-existing Asthma***).

~~Warnings~~WARNINGS

~~RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL, ANTI-INFLAMMATORY DRUG (NSAID) THERAPY~~
Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation
Serious GI 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 chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should

inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

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.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

~~ANAPHYLACTOID REACTIONS~~**Anaphylactoid Reactions**
As with other NSAIDS, ~~A~~anaphylactoid reactions may occur in patients without prior exposure to ~~etodolac~~Lodine. Lodine should not be given to patients with the aspirin triad. ~~The 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~~nonsteroidal anti-inflammatory drugs~~. Fatal reactions have been reported in such patients (see **~~Contraindications~~ CONTRAINDICATIONS** and **~~Precautions~~PRECAUTIONS, — General,** ***Pre-existing Asthma***). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

~~ADVANCED RENAL DISEASE~~**Advanced Renal Disease**
In cases with advanced kidney disease, treatment with Lodine is not recommended. However, if NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable ~~as with other NSAIDs, treatment with Lodine should only be initiated with close monitoring of the patient's kidney function~~ (see **~~Precautions—~~PRECAUTIONS, General,** ***Renal Effects***).

~~PREGNANCY~~**Pregnancy**
In late pregnancy, the third trimester, as with other NSAIDs, Lodine should be avoided because it may cause premature closure of the ductus arteriosus (see **~~Precautions—~~PRECAUTIONS, Pregnancy,** ***Teratogenic Effects—Pregnancy Category C***).

~~Precautions~~PRECAUTIONS

~~GENERAL PRECAUTIONS~~General

Lodine 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 solely if a decision is made to discontinue corticosteroids. The pharmacological activity of Lodine 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 Lodine. These laboratory abnormalities may disappear, remain essentially unchanged, or progress with continued 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 Lodine. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Lodine should be discontinued.

Renal Effects

Caution should be used when initiating treatment with Lodine in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with Lodine.

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with Lodine, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, ~~or~~ 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.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in ~~Adverse Reactions~~**ADVERSE REACTIONS**) may be attributable to these metabolites should be considered.

~~*Hepatic Effects*~~
~~Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including Lodine. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful 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 Lodine.~~

~~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 Lodine. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), Lodine should be discontinued.~~

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs including Lodine. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including Lodine, 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. Patients receiving Lodine who may be adversely affected by alteration 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, including Lodine. Therefore, as with other NSAIDs, Lodine should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma
~~About 10% of p~~Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas 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, ~~etodolac~~Lodine should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

~~INFORMATION FOR PATIENTS~~**Information For Patients**
Lodine, 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 symptom. Patients should be informed of the importance of this follow-up (see **WARNINGS, Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation).**

~~Physicians may wish to discuss with their patients the potential risks (see **WarningsPrecautions, Adverse Reactions**) and likely benefits of non-steroidal anti-inflammatory drug treatment.~~

Patients on Lodine (etodolac capsules and tablets) should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

~~Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see **Warnings** ,RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY THERAPY).~~

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see ~~**Warnings**~~ **WARNINGS**).

~~LABORATORY TESTS~~**Laboratory Tests**
Patients on long-term treatment with ~~Lodine, as with other~~ NSAIDs~~,~~ should have their CBC and a chemistry profile ~~hemoglobin or hematocrit~~ checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver or renal disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, Lodine should be discontinued.

~~DRUG INTERACTIONS~~**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 (see **PRECAUTIONS, General, *Renal Effects*)**.

Antacids
The concomitant administration of antacids has no apparent effect on the extent of absorption of Lodine. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

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

Cyclosporine, Digoxin, ~~Lithium,~~ Methotrexate
Lodine, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of cyclosporine, digoxin, ~~lithium, and~~ methotrexate, and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given Lodine, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Diuretics
Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide. Nevertheless, clinical studies, as well as postmarketing observations have shown that Lodine 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, General, *Renal Effects*),** as well as to assure diuretic efficacy.

Glyburide
Etodolac has no apparent pharmacokinetic interaction when administered with glyburide.

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.

Phenylbutazone
Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

Phenytoin
Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin.

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 that of users of either drug alone. Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and Lodine® (etodolac capsules and tablets) results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with Lodine as measured by prothrombin time. Thus, concomitant therapy with warfarin and Lodine should not require dosage adjustment of either drug. However, caution should be exercised because there have been a few spontaneous reports of prolonged prothrombin times, with or without bleeding, in ~~Lodine~~etodolac-treated patients receiving concomitant warfarin therapy. ~~Caution should be exercised because interactions have been seen with other NSAIDs.~~

~~DRUG/LABORATORY TEST INTERACTIONS~~**Drug/Laboratory Test Interactions**
The urine of patients who take Lodine can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with Lodine. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Lodine treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

~~CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY~~ **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the Lodine-treated cultures (50 to 200 μg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

~~PREGNANCY~~**Pregnancy**

Teratogenic Effects—Pregnancy Category C

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship. Animal reproduction studies are not always predictive of human response.

There are no adequate or well-controlled studies in pregnant women. Lodine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy, the third trimester, should be avoided.

~~LABOR AND DELIVERY~~**Labor and Delivery**

In rat studies with ~~etodolac~~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 Lodine on labor and delivery in pregnant women are unknown.

~~NURSING MOTHERS~~**Nursing Mothers**

It is not known whether etodolac 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 ~~etodolac~~Lodine, 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~~**Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

~~GERIATRIC POPULATION~~**Geriatric Use**

~~As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of Lodine were seen compared with the general population (see **Clinical Pharmacology** – PHARMACOKINETICS).~~In Lodine clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see **CLINICAL PHARMACOLOGY**, **Special Populations**).

Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on the gastrointestinal tract and kidneys) than younger patients (see **WARNINGS** and **PRECAUTIONS, General,** ***Renal Effects***). In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Therefore, caution should be exercised in treating the elderly and when increasing the dose (see **WARNINGS**).

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **PRECAUTIONS, General,** ***Renal Effects***).

~~Adverse Reactions~~ADVERSE REACTIONS

In patients taking Lodine 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.

Other events including: abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritis, rashes, tinnitus.

Adverse-reaction information for Lodine was derived from 2,629 arthritic patients treated with Lodine (etodolac capsules and tablets) in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with Lodine.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of Lodine b.i.d. (i.e., 600 to 1000 mg/day).

~~INCIDENCE GREATER THAN OR EQUAL TO 1%—PROBABLY CAUSALLY RELATED~~**Incidence Greater Than Or Equal To 1%—Probably Causally Related**
Body as a whole—Chills and fever.

Digestive system—Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

Nervous system—Asthenia/malaise*, dizziness*, depression, nervousness.

Skin and appendages—Pruritus, rash.

Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with Lodine.

Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked.

~~INCIDENCE LESS THAN 1%—PROBABLY CAUSALLY RELATED~~Incidence Less Than 1%—Probably Causally Related

(Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized.)

Body as a whole—*Allergic reaction, anaphylactic/anaphylactoid reactions (including shock).*

Cardiovascular system—Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system—Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation*, intestinal ulceration, pancreatitis.*

Hemic and lymphatic system—Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and nutritional—Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous system—Insomnia, somnolence.

Respiratory system—Asthma, *pulmonary infiltration with eosinophilia.*

Skin and appendages—Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis*, hyperpigmentation*, erythema multiforme.*

Special senses—Photophobia, transient visual disturbances.

Urogenital system—*Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

~~INCIDENCE LESS THAN 1%—CAUSAL RELATIONSHIP UNKNOWN~~**Incidence Less Than 1%—Causal Relationship Unknown**
(Medical events occurring under circumstances where causal relationship to Lodine is uncertain. These reactions are listed as alerting information for physicians.)

Body as a whole—Infection, headache.

Cardiovascular system—Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive system—Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional—Change in weight.

Nervous system—Paresthesia, confusion.

Respiratory system—Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages—Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses—Conjunctivitis, deafness, taste perversion.

Urogenital system—Cystitis, hematuria, leucorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

Additional Adverse Reactions Reported with NSAIDS

Body as a whole—Sepsis, death

Cardiovascular system—Tachycardia

Digestive system—Gastric ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis

Hemic and lymphatic system—Lymphadenopathy

Nervous system—Anxiety, dream abnormalities, convulsions, coma, hallucinations, meningitis, tremors, vertigo

Respiratory system—Respiratory depression, pneumonia

Urogenital system—Oliguria/polyuria, proteinuria

~~Overdosage~~OVERDOSAGE

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

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

~~Dosage and Administration~~DOSAGE AND ADMINISTRATION

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

Dosage adjustment of Lodine is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function~~.~~ (see ~~**Precautions — GENERAL PRECAUTIONS, *Renal Effects***~~ **PRECAUTIONS, General, *Renal Effects***).

~~ANALGESIA~~Analgesia

The recommended total daily dose of Lodine for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. ~~In some patients, if the potential benefits outweigh the risks, the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day.~~ Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

~~OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS~~ **Osteoarthritis and Rheumatoid Arthritis**

The recommended starting dose of Lodine for the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. ~~During long-term administration, the dose of Lodine may be adjusted up or down depending on the clinical response of the patient~~." A lower dose of 600 mg/day may suffice for long-term administration. ~~In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose~~. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with Lodine is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED

Lodine (etodolac capsules and tablets) is available as:

Lodine® (etodolac capsules) Capsules

200 mg capsules (light gray with one wide red band with LODINE 200/white with two narrow red bands)

—in bottles of 100, NDC 0046-0738-81

300 mg capsules (light gray with one wide red band with LODINE 300/light gray with two narrow red bands)

—in bottles of 100, NDC 0046-0739-81

Store at controlled room temperature 20°-25°C (68°-77°F), protected from moisture.

Lodine® (etodolac tablets) Tablets

400 mg tablets (yellow-orange, oval, film-coated tablet, debossed LODINE 400 on one side)

—in bottles of 100, NDC 0046-0761-81

Store at controlled room temperature 20°-25°C (68°-77°F).

Store tablets in original container until ready to use.

Dispense in light-resistant container.

500 mg tablets (blue, oval, film-coated tablet, branded LODINE 500 on one side)

—in bottles of 100, NDC 0046-0787-81

Store at controlled room temperature 20°-25°C (68°-77°F).

Store tablets in original container until ready to use.

Dispense in a light-resistant container.

The appearance of these capsules is a registered trademark of Wyeth Pharmaceuticals and the appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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