CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S-005

APPROVED DRAFT LABELING

Lodine® XL

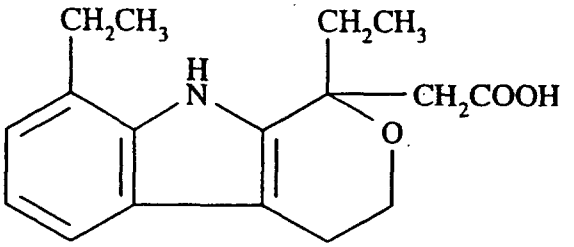
(etodolac extended-release tablets)

400 mg, 500 mg, 600 mg

DESCRIPTION

Lodine XL contains etodolac, which is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet contains etodolac for oral administration. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers. It is a white crystalline compound, insoluble in water, but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The chemical name is (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The molecular weight is 287.37. Its molecular formula is $C_{17}H_{21}NO_3$ and it has the following structural formula:



The inactive ingredients in Lodine XL include: dibasic sodium phosphate, ethylcellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, and titanium dioxide. In addition, the 400 mg tablets also contain FD&C Red #40, and FD&C Yellow #6 as color additives and polysorbate 80. The 500 mg tablets also contain D&C Yellow #10, FD&C Blue #2, and iron oxide as color additives and polysorbate 80. The 600 mg tablets also contain hydroxypropyl cellulose and iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Pharmacokinetics

Absorption

Lodine XL and Lodine both contain etodolac, but differ in their release characteristics. The systemic availability of etodolac from Lodine XL is generally greater than 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. After oral administration of Lodine XL in doses up to 800 mg once daily, peak concentrations occur approximately 6 hours after dosing and are dose proportional for both total and free etodolac. Peak concentrations following 1200 mg Lodine XL once daily were about 20% lower than that predicted by lower doses.

Table 1 shows the comparison of etodolac pharmacokinetic parameters after the administration of Lodine and Lodine XL.

Table 2 shows the etodolac pharmacokinetic parameters in various populations. The data from patients with renal and hepatic impairment were obtained following administration of (immediate-release) Lodine.

Table 1

Pharmacokinetic Parameters	Mean (CV)%† Lodine	Lodine XL
Extent of Oral Absorption (Bioavailability) [F]	≥ 80%	≥ 80%
Time to Peak Concentration (T_{max}), h	1.4 (61%)	6.7 (47%)
Oral Clearance (CL/F), mL/h/kg	49.1 (33%)	46.8 (37%)
Apparent Volume of Distribution (Vd/F), mL/kg	393 (29%)	566 (26%)
Terminal Half-life ($t_{1/2}$), h	6.4 (22%)	8.4 (30%)

†% Coefficient of variation

Table 2. Mean (CV%)† Pharmacokinetic Parameter Estimates of etodolac in Normal Healthy Adults and Various Special Populations

	Lodine XL				Lodine			
PK Parameters	Normal Healthy Adults (18-44)* (n=116)	Healthy Males (18-43) (n=102)	Healthy Females (25-44) (n=14)	Elderly (>65 yr) (66-88) (n=24)	Hemodialysis‡ (24-65) (n=9) Dialysis On	Dialysis Off	Renal Impairment‡ (46-73) (n=10)	Hepatic Impairment‡ (34-60) (n=9)
T_{max} h	6.7 (47%)†	6.8 (45%)	4.5 (56%)	6.2 (51%)	1.7 (88%)	0.9 (67%)	2.1 (46%)	1.1 (15%)
Oral Clearance (CL/F), mL/h/kg	46.8 (37%)	46.8 (37%)	47.2 (38%)	51.6 (40%)	NA	NA	58.3 (19%)	42.0 (43%)
Apparent Volume of Distribution (Vd/F), mL/kg	566 (26%)	580 (26%)	459 (28%)	552 (34%)	NA	NA	NA	NA
Terminal Half-life (t½), h	8.4 (30%)	8.4 (29%)	7.6 (45%)	7.8 (26%)	5.1 (22%)	7.5 (34%)	NA	5.7 (24%)

†% Coefficient of variation
* Age range (years)
‡ Pharmacokinetic parameters obtained following administration of Lodine
NA = not available

Food/Antacid Effects
Food has no significant effect on the extent of Lodine XL absorption, however, food significantly increased C_{max} (54%) following a 600 mg dose.

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

Distribution
The mean apparent volume of distribution (Vd/F) of etodolac following administration of Lodine XL is 566 mL/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin, and is independent of etodolac 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.

Metabolism
Etodolac metabolites do not contribute significantly to the pharmacological activity of Lodine XL.

Following administration of immediate-release etodolac, several 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 ^{14}C-etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylated-etodolac metabolites do 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 role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. The hydroxylated-etodolac metabolites undergo further glucuronidation followed by renal excretion and partial elimination in the feces.

Excretion
The mean oral clearance of etodolac following oral Lodine XL dosing is 47 (±17) mL/h/kg. The terminal half-life ($t_{1/2}$) of etodolac after Lodine XL administration is 8.4 hours compared to 6.4 hours for Lodine. Approximately 1% of a Lodine dose is excreted unchanged in the urine, with 72% of the dose excreted into the urine as parent drug plus metabolites:

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

Fecal excretion accounted for 16% of the dose.

Special Populations

Geriatric
In clinical studies, etodolac clearance was reduced by about 15% in older patients (> 65 years of age). In these studies, age was not shown to have any effect on half-life or protein binding, and demonstrated no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, as they may be more sensitive to antiprostaglandin effects than younger patients (see **PRECAUTIONS–Geriatric Use**).

Pediatric

~~Lodine XL has not been investigated in pediatric patients.~~

The pharmacokinetics of Lodine XL were assessed in an open-label, 12-week clinical trial. Seventy-two (72) patients, aged 6 to 16 years old, with juvenile rheumatoid arthritis, received Lodine XL in doses of 13.3 to 21.3 mg/kg given as 400 to 1000 mg once daily. Pharmacokinetic data from 59 patients in this study exhibited pharmacokinetic disposition of Lodine XL similar to that seen in healthy adults.

Table 3. Pharmacokinetic Parameter Estimates for Lodine XL in Patients with Juvenile Rheumatoid Arthritis

Parameter	JRA [a] (Age: 6-16) [b] n=59
Oral Clearance (CL/F), mL/h/kg	47.8 (38%)
Apparent Volume of Distribution (Vd/F), mL/kg	789 (61%)
Half-life (t½), h	12.1 (75%)

a: Mean (CV) of parameter estimates predicted from population pharmacokinetics
b: Age range (years)

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 Insufficiency

The pharmacokinetics of etodolac following administration of Lodine XL have not been investigated in subjects with hepatic insufficiency. Following administration of Lodine, the plasma protein binding and disposition of total and free etodolac were unchanged in the presence of compensated hepatic cirrhosis. Although no dosage adjustment is generally required in patients with chronic hepatic diseases, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure.

Renal Insufficiency

The pharmacokinetics of etodolac following administration of Lodine XL have not been investigated in subjects with renal insufficiency. Etodolac renal clearance following administration of Lodine was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance, 37 to 88 mL/min). 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. Etodolac plasma protein binding decreases in patients with severe renal deficiency. Etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

CLINICAL TRIALS

Arthritis

The use of Lodine XL in managing the signs and symptoms of osteoarthritis of the knee and rheumatoid arthritis was assessed in double-blind, randomized, parallel, controlled clinical trials in 1552 adult patients. In these trials, Lodine XL in doses of 400 mg to 1200 mg, given once daily, provided efficacy comparable to etodolac given 300 mg b.i.d. to 400 mg t.i.d.

The safety, efficacy, and pharmacokinetics of Lodine XL were assessed in an open-label, 12-week clinical trial. Seventy-two (72) patients, aged 6 to 16 years old, with juvenile rheumatoid arthritis, received Lodine XL in doses of 400 to 1000 mg (13.3 – 21.3 mg/kg body weight) once daily. At these doses, Lodine XL controlled the signs and symptoms of juvenile rheumatoid arthritis. Based on the results of this study, the safety profile of Lodine XL (at doses not exceeding 20 mg/kg) appeared to be similar to that observed in the adult arthritic patients in clinical trials. (See **PRECAUTIONS–Pediatric Use.**)

INDICATIONS AND USAGE

Lodine XL is indicated:

For the management of the signs and symptoms of osteoarthritis.

For the management of the signs and symptoms of rheumatoid arthritis.

CONTRAINDICATIONS

Lodine XL is contraindicated in patients with known hypersensitivity to etodolac. Lodine XL 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 have been reported in such patients (see **WARNINGS–Anaphylactoid Reactions**, and **PRECAUTIONS** - *Pre-existing 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 1 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 Lodine XL. Lodine XL 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** - *Pre-existing Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease
In cases with advanced kidney disease, treatment with Lodine XL 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, Lodine XL should be avoided because it may cause premature closure of the ductus arteriosus (see **PRECAUTIONS** - *Nonteratogenic Effects*).

PRECAUTIONS

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

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

Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS–Advanced Renal Disease**).

As with other NSAIDs, long-term administration of Lodine XL 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-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 nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Lodine XL 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 Lodine XL. 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 XL, should have their hemoglobin or hematocrit checked if they develop 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 XL 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, Lodine XL should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing 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, Lodine XL should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Information for Patients
Lodine XL, 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**).

Patients 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 case of an anaphylactoid reaction (see **WARNINGS**).

In late pregnancy, as with other NSAIDs, Lodine XL should be avoided because it may 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, Lodine XL should be discontinued.

Drug Interactions

Aspirin

When etodolac 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 etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

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 etodolac 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 etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and Lodine XL should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Methotrexate

Etodolac has no apparent pharmacokinetic interaction with methotrexate. However, 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.

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 XL 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. With NSAIDs, 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.

Cyclosporine, Digoxin
Lodine XL, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs, leading to elevated serum levels of cyclosporine and digoxin and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given Lodine XL, 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.

Phenylbutazone
Phenylbutazone causes an 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 co-administration of phenylbutazone, it is not recommended that they be co-administered.

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

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

Drug/Laboratory Test Interactions
The urine of patients who take etodolac 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 etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac 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
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 18 months or 2 years, 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% to 5% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 g/mL) compared to negative controls (2%); 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

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 XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the 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 Lodine XL 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 Lodine XL, 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 have not been established.~~

If a decision is made to use Lodine XL for patients six years of age or older, as with other NSAIDs, such patients should be monitored periodically. (See **PRECAUTIONS–Laboratory Tests** and **CLINICAL TRIALS–Arthritis**).

Geriatric Use
As with any NSAID, caution should be exercised in treating the elderly (65 years and older). In patients 65 years and older, no substantial differences in the side effect profile of Lodine XL were seen compared with the general population (see **CLINICAL PHARMACOLOGY–Pharmacokinetics**).

ADVERSE REACTIONS
A total of 1552 patients were exposed to Lodine XL in controlled clinical studies of at least 4 weeks in length and using daily doses in the range of 400 to 1200 mg. In the tabulations below, adverse event rates are generally categorized based on the incidence of events in the first 30 days of treatment with Lodine XL. As with other NSAIDs, the cumulative adverse event rates may increase significantly over time with extended therapy.

In patients taking NSAIDs, including Lodine XL, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

gastrointestinal experiences including:

abdominal pain	constipation	diarrhea
dyspepsia	flatulence	GI ulcers (gastric/duodenal)*
gross bleeding/perforation*	nausea	vomiting

other events including:

abnormal renal function*	anemia*	asthenia
dizziness	edema*	elevated liver enzymes*
headaches	hypertension	increased bleeding time*
infection	pharyngitis	pruritus
rashes	rhinitis	tinnitus*

*Adverse events that were observed in < 1% of patients in the first 30 days of treatment with Lodine XL in clinical trials.

Additional NSAID Adverse Experiences Reported Occasionally with NSAIDS or Lodine XL Include:

Body as a whole –
allergic reaction, anaphylactoid reaction, chills, fever, sepsis

Cardiovascular system –
congestive heart failure, flushing, palpitations, tachycardia, syncope, vasculitis (including necrotizing and allergic)

Digestive system –
anorexia, cholestatic hepatitis, cholestatic jaundice, dry mouth, duodenitis, eructation, esophagitis, gastritis, gastric/peptic ulcers, glossitis, hepatic failure, hepatitis, hematemesis, intestinal ulceration, jaundice, liver necrosis, melena, pancreatitis, rectal bleeding, stomatitis

Hemic and lymphatic system –
agranulocytosis, ecchymosis, eosinophilia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, purpura, thrombocytopenia

Metabolic and nutritional –
hyperglycemia in previously controlled diabetic patients

Nervous system –
anxiety, confusion, depression, dream abnormalities, insomnia, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory system –
asthma, dyspnea

Skin and appendages –
angioedema, cutaneous vasculitis with purpura, erythema multiforme, hyperpigmentation, sweating, urticaria, vesiculobullous rash

Special senses –
blurred vision, photophobia, transient visual disturbances

Urogenital system –
dysuria, elevated BUN, oliguria/polyuria, proteinuria, renal failure, renal insufficiency, renal papillary necrosis, serum creatinine increase, urinary frequency

Other NSAID Adverse Reactions, Which Occur Rarely Are:

Body as a whole –
anaphylactic reactions, appetite changes, death

Cardiovascular system –
arrhythmia, cerebrovascular accident, hypotension, myocardial infarction

Digestive system –
colitis, esophagitis with or without stricture or cardiospasm, thirst, ulcerative stomatitis

Hemic and lymphatic system –
aplastic anemia, lymphadenopathy

Metabolic and nutritional –
change in weight

Nervous system –
coma, convulsions, hallucinations, meningitis

Respiratory –
bronchitis, pneumonia, respiratory depression, sinusitis

Skin and appendages –
alopecia, exfoliative dermatitis, maculopapular rash, photosensitivity, skin peeling, Stevens-Johnson syndrome, toxic epidermal necrosis

Special senses –
conjunctivitis, deafness, hearing impairment, taste perversion

Urogenital System –
cystitis, hematuria, interstitial nephritis, leukorrhea, renal calculus, uterine bleeding irregularities

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

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 XL, the dose and frequency should be adjusted to suit an individual patient's needs.

For the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis, the recommended starting dose of Lodine XL is 400 to 1000 mg, given once daily. As with other NSAIDs, the lowest effective dose should be sought for each patient. During long-term administration, the dose of Lodine XL may be adjusted up or down, depending on the patient's clinical response, up to a maximum dose of 1200 mg/day. Doses above 1200 mg/day have not been studied, and thus a dose-efficacy relationship at doses beyond 1200 mg/day has not been established. In chronic conditions, a therapeutic response to therapy with Lodine XL is sometimes seen within one week of therapy, but most often is observed by two weeks.

HOW SUPPLIED

Lodine XL® (etodolac extended-release tablets) is available as:

400 mg tablets (orange-red, capsular-oval shaped, biconvex film-coated tablet, branded LODINE XL 400 on one side)
- in bottles of 100, NDC 0046-0829-81
- in unit-dose packages of 100, NDC 0046-0829-99

500 mg tablets (grey-green, capsular-oval shaped, biconvex film-coated tablet, branded LODINE XL 500 on one side)
- in bottles of 100, NDC 0046-0839-81
- in unit-dose packages of 100, NDC 0046-0839-99

600 mg tablets (light grey, capsular-oval shaped, biconvex film-coated tablet, branded LODINE XL 600 on one side)
- in bottles of 100, NDC 0046-0831-81
- in unit-dose packages of 100, NDC 0046-0831-99

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]
Protect from excessive heat and humidity.

Caution: Federal law prohibits dispensing without prescription.
CI 4848-3
Issued (DATE)
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