

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zipsor™ safely and effectively. See full prescribing information for Zipsor.

Zipsor™ (diclofenac potassium) Liquid Filled Capsules
Initial U.S. Approval: [1998]

WARNING

See full prescribing information for complete boxed warning.

- **Cardiovascular Risk**
 - NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)
 - Zipsor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4)
- **Gastrointestinal Risk**
 - NSAIDs cause an increased risk of serious gastrointestinal adverse events including, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)

INDICATIONS AND USAGE

Zipsor is a nonsteroidal anti-inflammatory drug indicated for relief of mild to moderate acute pain. (1)

DOSAGE AND ADMINISTRATION

The dosage is 25 mg four times a day. (2)

DOSAGE FORMS AND STRENGTHS

- 25 mg Liquid Filled Capsule (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac. (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
- Use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery. (4)
- Zipsor contains gelatin and should not be given to patients with known hypersensitivity to bovine protein. (4)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke can occur with NSAID treatment. The lowest possible dose of Zipsor should be used in patients with known CV disease or risk factors for CV disease. (5.1)
- NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation. Zipsor should be prescribed with caution in those with a prior history of ulcer disease or gastrointestinal bleeding. (5.2)

- Elevation of one or more liver tests may occur during therapy with diclofenac. Zipsor should be discontinued immediately if abnormal liver tests persist or worsen. (5.3)
- Hypertension can occur with NSAID treatment. Blood pressure should be monitored closely during treatment with Zipsor. (5.4)
- Fluid retention and edema have been observed in some patients taking NSAIDs. Zipsor should be used with caution in patients with fluid retention or heart failure. (5.5)
- Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. Zipsor should be used with caution in patients at greatest risk of this reaction, including the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and ACE inhibitors. (5.6)
- Anaphylactoid reactions may occur in patients with the aspirin triad or in patients without prior exposure to Zipsor and should be discontinued immediately if an anaphylactoid reaction occurs. (5.7)
- NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Zipsor should be discontinued if rash or other signs of local skin reaction occur. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 1% of Zipsor 25 mg treated subjects) are gastrointestinal experiences including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Xanodyne Pharmaceuticals, Inc. at 1-877-773-7793 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects including increased GI bleeding. (7.1)
- Concomitant use of anticoagulants and diclofenac have a risk of serious GI bleeding higher than users of either drug alone. (7.2)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm. Based on human data, starting at 30 weeks gestation, Zipsor should be avoided as premature closure of the ductus arteriosus in the fetus may occur. (5.9, 8.1)
- **Nursing Mothers:** Use with caution, as it is not known if diclofenac is excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see Warnings and Precautions (5.1)].**
- **Zipsor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4)].**

Gastrointestinal Risk

NSAIDs increase the risk of serious gastrointestinal (GI) adverse reactions including, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see Warnings and Precautions (5.2)].

1. INDICATIONS AND USAGE

Zipsor is indicated for relief of mild to moderate acute pain in adults (18 years of age or older).

2. DOSAGE AND ADMINISTRATION

2.1 Initiating Therapy

For treatment of mild to moderate acute pain, the dosage is 25 mg four times a day. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

2.2 Non-Interchangeability with Other Formulations of Diclofenac

Different formulations of oral diclofenac are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulation of diclofenac to Zipsor. The only approved dosing regimen for Zipsor is 25 mg four times a day.

3. DOSAGE FORMS AND STRENGTHS

Oral Liquid Filled Capsule 25 mg

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4. CONTRAINDICATIONS

Zipsor is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to diclofenac. [see Warnings and Precautions (5.7, 5.8)].

Zipsor is contraindicated in 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 and Precautions (5.7 and 5.13)].

Zipsor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)].

Zipsor contains gelatin and is contraindicated in patients with known hypersensitivity to bovine protein.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Inform patients about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see Contraindications (4)].

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as diclofenac, does increase the risk of serious GI events [see Warnings and Precautions (5.2)].

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

NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) adverse events including, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue with longer duration

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of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term NSAID therapy is not without risk.

Prescribe NSAIDs, including Zipsor, with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during Zipsor therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of Zipsor until a serious GI adverse event is ruled out. For high risk patients, alternative therapies that do not include NSAIDs, should be considered.

5.3 Hepatic Effects

Borderline elevations (less than 3 times the upper limit of the normal [ULN] range) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients in clinical trials of indications other than acute pain. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials of a diclofenac - misoprostol combination product, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In an open-label, controlled trial of 3,700 patients treated for 2–6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of the 3,700 patients and included marked elevations (>8 times the ULN) in about 1% of the 3,700 patients. In this open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis. Almost all meaningful elevations in transaminases were detected before patients became symptomatic.

Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations. In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of NSAID therapy.

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Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

In a European retrospective population-based, case-controlled study, 10 cases of diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female gender, doses of 150 mg or more, and duration of use for more than 90 days.

Physicians should measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), discontinue Zipsor immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver-related event in patients treated with Zipsor, use the lowest effective dose should be used for the shortest duration possible. Exercise caution when prescribing Zipsor with concomitant drugs that are known to be potentially hepatotoxic (e.g. acetaminophen, certain antibiotics, antiepileptics). Caution patients to avoid taking unprescribed acetaminophen while using Zipsor.

5.4 Hypertension

NSAIDs, including diclofenac, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including Zipsor, with caution in patients with hypertension. Monitor blood pressure (BP) closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use Zipsor with caution in patients with fluid retention or heart failure.

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5.6 Renal Effects

Use caution when initiating treatment with Zipsor in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

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

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Zipsor. Zipsor is contraindicated in 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 Warnings and Precautions).

5.8 Adverse Skin Reactions

NSAIDs, including diclofenac, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations, and to discontinue Zipsor at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

Starting at 30 weeks gestation, Zipsor, as with other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur.

5.10 Corticosteroid Treatment

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

5.11 Masking of Inflammation and Fever

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

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5.12 Hematological Effects

Anemia may occur in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients on long-term therapy with NSAIDs, including diclofenac, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss. Zipsor is not indicated for long-term treatment.

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. Carefully monitor patients treated with Zipsor who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.13 Use in Patients with Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, Zipsor is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

5.14 Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. For patients on long-term treatment with NSAIDs, periodically check a CBC and a chemistry profile. Discontinue Zipsor if abnormal liver tests or renal tests persist or worsen. Zipsor is not indicated for long-term treatment.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events [see Boxed Warning and Warnings and Precautions (5.1)]
- Gastrointestinal effects [see Boxed Warning and Warnings and Precautions (5.2)]
- Hepatic effects [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Congestive heart failure and edema [see Warnings and Precautions (5.5)]
- Renal effects [see Warnings and Precautions (5.6)]
- Anaphylactoid reactions [see Warnings and Precautions (5.7)]
- Serious skin reactions [see Warnings and Precautions (5.8)]

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with the rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Zipsor was evaluated in 965 subjects. In patients treated with Zipsor 25 mg (N=345) or a higher dose, three or four times a day, for 4 to 5 days, the most common adverse reactions (i.e., reported in $\geq 1\%$ of Zipsor treated patients) were as follows: gastrointestinal

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experiences including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating. (see Table 1)

Table 1

Incidence of Treatment Emergent Adverse Reactions with Incidence \geq 1% of Zipsor Treated Patients in Multiple-Dose Studies

MedDRA System Organ Class and Preferred Term	Zipsor* 25 mg n=345 n (%)	Placebo* n=327 n (%)
Any Adverse Events	144 (41.7)	181 (55.4)
Abdominal Pain	24 (7.0)	11 (3.4)
Constipation	11 (3.2)	9 (2.8)
Diarrhea	8 (2.3)	9 (2.8)
Dyspepsia	4 (1.2)	8 (2.4)
Nausea	57 (16.5)	66 (20.2)
Vomiting	20 (5.8)	26 (8.0)
Dizziness	12 (3.5)	17 (5.2)
Headache	43 (12.5)	56 (17.1)
Somnolence	9 (2.6)	6 (1.8)
Pruritus	5 (1.4)	6 (1.8)
Sweating Increase	4 (1.2)	2 (0.6)

*There was greater use of concomitant opioid rescue medication in placebo treated patients than in Zipsor treated patients.

In patients taking 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) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

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Additional adverse experiences reported in patients taking other NSAIDs 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 bleeding, glossitis, hematemesis, hepatitis, jaundice

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, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System: asthma, dyspnea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions in patients taking other NSAIDs, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes, death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, 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 System: respiratory depression, pneumonia

Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment

7. DRUG INTERACTIONS

7.1 Aspirin

When administered with aspirin, diclofenac's protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Zipsor and aspirin is not generally recommended because of the potential of increased adverse effects.

7.2 Anticoagulants

The effects of anticoagulants such as 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 with use of either drug alone.

7.3 ACE-inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking Zipsor concomitantly with ACE-inhibitors.

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7.4 Diuretics

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy of Zipsor and diuretics, observe patients closely for signs of renal failure [see Warnings and Precautions (5.6)], as well as to assure diuretic efficacy.

7.5 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 Zipsor and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when Zipsor is administered concomitantly with methotrexate.

7.7 Cyclosporine

Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Zipsor may increase cyclosporine's nephrotoxicity. Use caution when Zipsor is administered concomitantly with cyclosporine.

7.8 Inhibitors or Substrates of Cytochrome P450 2C9 Other Considerations

Diclofenac is metabolized predominantly by cytochrome P450 2C9. Co-administration of diclofenac with another drug medication known to be metabolized by or that which inhibits Cytochrome P450 2C9 may unpredictably affect the pharmacokinetics of diclofenac or the co-administered drug medication. Caution should be used to evaluate each patient's medical history when consideration is given to prescribing Zipsor [see Clinical Pharmacology ([12.3](#))].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.

Starting at 30 weeks gestation, Zipsor, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Zipsor can cause fetal harm when administered to a pregnant woman starting at 30 weeks gestation. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus. There are no adequate and well-controlled studies in pregnant women. Prior to 30 weeks gestation, Zipsor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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Reproductive studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day or 60 mg/m²/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day or 60 mg/m²/day for rats, and 80 mg/m²/day for rabbits, 1-fold and 2-fold an adult human daily dose of 100 mg/day, respectively), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice, rats, and humans.

Literature studies have shown that diclofenac has been shown to exert direct teratogenic effects on rat embryos in vitro at concentrations of 7.5 and 15 µg/mL, and diclofenac exposure to pregnant rats (1 mg/kg, IP) can lead to prolonged gestation as well as liver toxicity and neuronal loss in offspring.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk; however, there is a case report in the literature indicating that diclofenac can be detected at low levels in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Zipsor, 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.

8.4 Pediatric Use

The safety and effectiveness of Zipsor in pediatric patients has not been established.

8.5 Geriatric Use

Clinical studies of Zipsor did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

Diclofenac is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. 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. Older age increases the risk for GI 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 [see 5.2 Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation].

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10. OVERDOSAGE

Symptoms following acute NSAID overdoses include 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.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. 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, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11. DESCRIPTION

Zipsor (diclofenac potassium) Liquid Filled Capsule is a benzeneacetic acid derivative NSAID. Zipsor is available as liquid-filled, capsules of 25 mg for oral administration. The chemical name is 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid monopotassium salt. The molecular weight is 334.24. Its molecular formula is $C_{14}H_{10}Cl_2NKO_2$, and it has the following structural formula.



The inactive ingredients in Zipsor include ProSorb® (a proprietary combination of polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, and hydrochloric acid), isopropyl alcohol, and mineral oil. The capsule shells contain gelatin, sorbitol, isopropyl alcohol, glycerin, and mineral oil. The imprinting on the gelatin capsules is black edible ink.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zipsor is an NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Zipsor, like that of other NSAIDs, is not completely understood but may involve inhibition of the cyclooxygenase (COX-1 and COX-2) pathways.

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Diclofenac's mechanism may also be related to prostaglandin synthetase inhibition. The analgesic mechanism of action needs further elucidation.

12.3 Pharmacokinetics

The pharmacokinetics of Zipsor was assessed in 24 healthy, normal volunteers who received 25 mg Zipsor under fasting conditions. The mean pharmacokinetic parameters for Zipsor are shown in Table 2.

Table 2
Mean Pharmacokinetics of Zipsor

PK Parameter	Number of Subjects	Mean ± Standard Deviation
T _{max} (hr)	24	0.47 ± 0.17
Terminal Half-life (hr)	24	1.07 ± 0.29
C _{max} (ng/mL)	24	1087 ± 419
AUC(0-∞) (ng·h/mL)	24	597 ± 151

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. After repeated oral administration, no accumulation of diclofenac in plasma occurred.

The extent of diclofenac absorption is not significantly affected when Zipsor is taken with food. However, the rate of absorption is reduced by food, as indicated by a two-fold increase of T_{max} and a 47% decrease in C_{max}.

Distribution

The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 µg/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy- diclofenac. In patients with

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renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 1 hour.

Special Populations

Pediatric: The pharmacokinetics of Zipsor has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Impairment: Hepatic metabolism accounts for almost 100% of diclofenac elimination, so patients with hepatic disease may require reduced doses of Zipsor compared to patients with normal hepatic function.

Renal Impairment: Diclofenac pharmacokinetics has been investigated in subjects with renal insufficiency. In patients with renal impairment (inulin clearance 60-90, 30-60, and <30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (or 12 mg/m²/day, 0.2-fold an adult human daily dose of 100 mg/day) have revealed no significant increase in tumor incidence. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m²/day, 0.014-fold an adult human daily dose of 100 mg/day) in males and 1 mg/kg/day (3 mg/m²/day, 0.04-fold an adult human daily dose of 100 mg/day) in females did not reveal any oncogenic potential.

Mutagenesis: Diclofenac sodium did not show mutagenic activity in in vitro point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian in vitro and in vivo tests, including dominant lethal and male germinal epithelial chromosomal aberration studies in Chinese hamsters.

Impairment of Fertility: Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/m²/day, 0.4-fold an adult human daily dose of 100 mg/day) did not affect fertility.

14. CLINICAL STUDIES

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The efficacy of Zipsor was demonstrated in two multicenter, randomized, double-blind, placebo-controlled, parallel arm, multiple-dose clinical trials comparing Zipsor 25 mg and placebo in patients with pain following bunionectomy with osteotomy. Once patients met the criteria for randomization (pain intensity ≥ 4 on a 0-10 numerical pain rating scale) they received their initial dose of study medication followed by a remedication dose when requested by the patient, and were then dosed every six hours over four days. Pain intensity was recorded at 3 and 6 hours postdose during the fixed dosing period. . In Study 1, mean baseline pain intensity scores were 6.9 in the Zipsor group (range: 4 – 10) and 7.3 in the placebo group (range: 4 – 10). In both studies, patients treated with Zipsor had a lower mean pain intensity score over the 48-hour inpatient period following the first remedication dose (see Figure 1).. The median time to onset of pain relief was less than one hour for Zipsor 25 mg across the clinical trials.

The results were similar in Study 2.

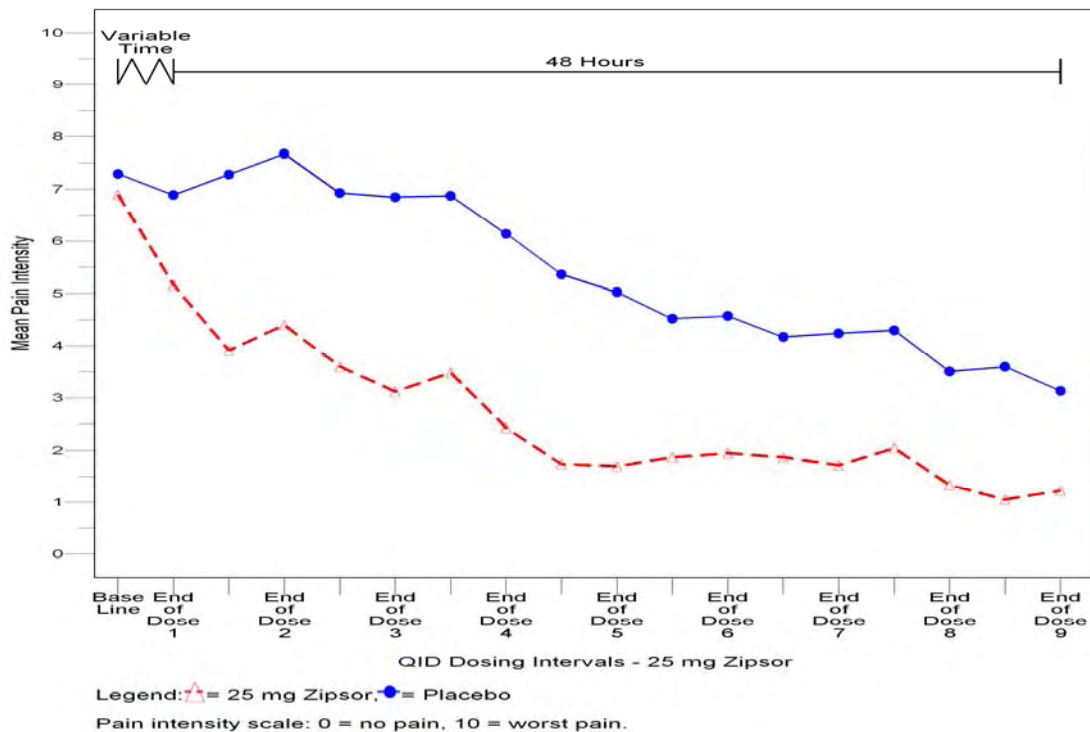


Figure 1 Mean Pain Intensity Scores at the Midpoint and End of Each Dose Interval in Postbunionectomy Pain Study 1

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16. HOW SUPPLIED/STORAGE AND HANDLING

Zipsor 25 mg is supplied as translucent, pale yellow, liquid-filled, capsules printed with "X592" in black ink. Bottles of 100 Capsules NDC# 66479-592-10.

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]
Protect from moisture.

Dispense in tight container (USP).

17. PATIENT COUNSELING INFORMATION

Inform patients should be informed of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and instructed them to read the NSAID Medication Guide prior to using Zipsor [see Medication Guide (17.9)].

17.1 Cardiovascular Effects

NSAIDs, including diclofenac, may cause serious CV events, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, advise patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up [see Warnings and Precautions (5.1)].

17.2 Gastrointestinal Effects

NSAIDs, including diclofenac, can cause GI discomfort and, rarely, more serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, advise patients to be alert for the signs and symptoms of ulcerations and bleeding, and to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Inform patients of the importance of this follow-up [see Warnings and Precautions (5.2)].

17.3 Hepatotoxicity

Inform patients 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, instruct patients to stop therapy with Zipsor and seek immediate medical therapy [see Warnings and Precautions (5.3)].

17.4 Adverse Skin Reactions

NSAIDs can cause serious skin reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, advise patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop Zipsor immediately if they develop any type of rash and contact their physicians as soon as possible [see Warnings and Precautions (5.8)].

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17.5 Weight Gain and Edema

Advise patients to promptly report to their physicians signs or symptoms of unexplained weight gain or edema during treatment with Zipsor [see Warnings and Precautions (5.5)].

17.6 Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Warnings and Precautions (5.7)].

17.7 Effects During Pregnancy

Starting at 30 weeks gestation, Zipsor and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. [see Use in Specific Populations ([8.1](#))]

Marketed by:

 **Xanodyne**[®]
pharmaceuticals, inc.

Newport, KY

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

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

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant, **NSAID medicines should not be used past 30 weeks of pregnancy.**
- if you are breastfeeding, **talk to your doctor.**

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

Serious side effects include:	Other side effects include:
<ul style="list-style-type: none">• heart attack• stroke• high blood pressure• heart failure from body swelling (fluid retention)• kidney problems including kidney failure• bleeding and ulcers in the stomach and intestine• low red blood cells (anemia)• life-threatening skin reactions• life-threatening allergic reactions• liver problems including liver failure• asthma attacks in people who have asthma	<ul style="list-style-type: none">• stomach pain• constipation• diarrhea• gas• heartburn• nausea• vomiting• dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Xanodyne Pharmaceuticals, Inc. at 1-877-773-7793.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Trade Name
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol), Flector, Zipsor
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, *Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

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