

Nocturnal Hypoglycemia Marker Looks Possible

BY JANE SALODOF MACNEIL

Fasting plasma glucose variability could be a marker for risk of nocturnal hypoglycemia, according to an analysis of data from more than 7,500 patients treated with insulin detemir for type 1 or type 2 diabetes.

Changes in the coefficient of variance for fasting plasma glucose (CV FPG) correlated with changes in nocturnal hypo-

glycemia, Dr. Leo Niskanen of Kuopio (Finland) University Hospital, and his coinvestigators reported in the journal *Diabetes Research and Clinical Practice* (doi:10.1016/j.diabres.2009.08.005).

When patients had less FPG variability after 3 months on insulin detemir (Levemir), the incidence of nocturnal hypoglycemia also was reduced. This was true of both types of diabetes, and was independent of im-

provement in metabolic control.

“Our results suggest CV FPG can be a useful marker for risk of nocturnal hypoglycemia in the clinical setting, and that glucose instability can be gauged quite simply with home FPG monitoring,” the authors wrote in their conclusion.

They also speculated that reduced variability “may have contributed to the simultaneous improvement of metabolic control and reduction of nocturnal hypo-

glycemia observed with detemir therapy” in the study.

The analysis was based on the PRE-DICTIVE study (Predictable Results and Experience in Diabetes Through Intensification and Control to Target: an International Variability Evaluation), a multinational observational investigation sponsored by Novo Nordisk, maker of detemir, that had more than 19,000 patients (*Int. J. Clin. Pract.* 2007;61:523-8; *Diabetes Obes. Metab.* 2007;9:428-34).

In the analysis of the relationship between FPG variability and nocturnal hypoglycemia, there were 1,433 type 1 diabetes patients with nocturnal hypoglycemia at baseline and 2,170 without. Among patients with type 2 diabetes, 553 had nocturnal hypoglycemia at baseline, while 3,365 did not.

The incidence of nocturnal hypoglycemia at baseline and 3 months later was based on patient reports. At both time points, patients were asked whether they had had nocturnal hypoglycemic events during the previous 4 weeks.

After 3 months on detemir, the percentage of patients with nocturnal hypoglycemia decreased significantly—from 39.8% to 14.7% of patients with type 1 diabetes and from 14.1% to 3.0% of patients with type 2. The average number of nocturnal hypoglycemia events over 4 weeks also fell from 3.1 to 2.1 for type 1 patients and from 2.7 to 1.9 for type 2.

The investigators found these declines to be correlated with changes in FPG variability. At 3 months, the patients with nocturnal hypoglycemia had significantly higher CV FPG than those who did not report nocturnal hypoglycemia—32.8% vs. 23.0% in the type 1 group and 20.7% vs. 12.7% in the type 2 group.

“These absolute values were similar to baseline, although the [nocturnal hypoglycemia positive] subgroups had decreased in patient number,” they wrote.

The analysis also identified demographic differences between patients who reported nocturnal hypoglycemia at baseline and those who did not. In the type 1 population, patients reporting nocturnal hypoglycemia were significantly more likely to be female (60.4% vs. 50.2%), were older (44.1 years vs. 42.2 years), had a longer duration of diabetes (18.9 years vs. 16.3 years), and had lower FPG (9.1 mmol/L vs. 9.4 mmol/L) than those not reporting nocturnal hypoglycemia.

In the type 2 population, patients reporting nocturnal hypoglycemia were not significantly different in terms of gender or age, but had a significantly longer duration of diabetes (13.7 years vs. 12.7 years), weighed less (86.2 kg vs. 91.7 kg), had a lower HbA_{1c} (7.9% vs. 8.2%), and had a lower FPG (8.9 mmol/L vs. 9.7 mmol/L).

Dr. Niskanen disclosed receiving speaker fees and research funds from Novo Nordisk. Two of his coauthors are employees of the company, and one owns shares in Novo Nordisk. ■

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
These highlights do not include all the information needed to prescribe Zipsor™ (diclofenac potassium) Liquid Filled Capsule safely and effectively. See Zipsor Full Prescribing Information for complete usage and safety data. Zipsor™ (diclofenac potassium) Liquid Filled Capsule Rx Only Initial U.S. Approval: [1998]

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].**
- **Zipsor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications].**
- **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].**

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

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

Zipsor is contraindicated in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients [see Warnings and Precautions].

Zipsor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions]. Zipsor contains gelatin and is contraindicated in patients with known hypersensitivity to bovine protein.

WARNINGS AND PRECAUTIONS

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].

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].

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 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. **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. 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 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.

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.

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.

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.

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).

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 signs of hypersensitivity.

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.

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.

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.

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.

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.

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.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular thrombotic events and gastrointestinal effects [see Boxed Warning and Warnings and Precautions]; hepatic effects, hypertension, congestive heart failure and edema, renal effects, anaphylactoid reactions, and serious skin reactions [see Warnings and Precautions]

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 ≥ 1% of treated patients) were as follows: gastrointestinal experiences including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating.

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, headache, increased bleeding time, pruritus, rashes, and tinnitus.

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;

ity, 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

DRUG INTERACTIONS

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. **Anticoagulants**—The effects of anticoagulants such as 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. **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. **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.

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. **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. **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. **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 in full Prescribing Information].

USE IN SPECIFIC POPULATIONS

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.

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.

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.

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.

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

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

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.

Inform patients of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and instruct them to read the NSAID Medication Guide prior to using Zipsor.

Marketed by: **Xanodyne**
pharmaceuticals, Inc. Newport, KY

Brief Summary of PI-592-A Rev. 06/2009 ZPPPO 309-2506

Zipsor is a registered trademark of Xanodyne® Pharmaceuticals, Inc. © 2009 Xanodyne® Pharmaceuticals, Inc., Newport, KY 41071. All rights reserved.