

ACGME Feels Heat on Work Hours Restrictions

BY ALICIA AULT

A new advocacy coalition is putting pressure on the Accreditation Council for Graduate Medical Education to speed up its process of developing new recommendations on work hour restrictions for residents, and to closely follow the Institute of Medicine's recommendations by further reducing hours.

The coalition, led by Public Citizen, sent a letter to Dr. Thomas J. Nasca, ACGME's executive director, urging the accrediting body to adopt rules that aim to reduce sleep deprivation and to better protect patients, Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, said in a briefing with reporters. "The available evidence suggests that the public is deeply concerned about the current work hours of medical resi-

dents," as stated in the letter to Dr. Nasca. The letter is posted at www.wake-updoctor.org.

At the briefing, Dr. John Ingell, a surgical resident at the University of New Mexico, Albuquerque, said that he noticed he became less compassionate when severely fatigued. Concentration also suffered, said Dr. Ingell, who is on the board of the Service Employees International Union's medical resident section.

Dan Henderson, a medical student at the University of Connecticut, Farmington, said that at the time, he was proud to work 12 hours or more a day or a 30-hour continuous shift on his surgical rotation. Now, he feels "ashamed," because he realizes that such efforts did not improve his education and also had a negative effect on his feelings for patients.

He said he supported the limit on work hours recommended by the IOM in 2008. The IOM urged a reduction from 30-hour shifts to shifts lasting no longer than 16 hours. "I really think medicine needs a wake-up call and needs to move into the 21st century," said Mr. Henderson.

The ACGME had planned on reviewing the work hours 5 years after they were first reduced, which happened to coincide with the IOM's report, said Dr. Nasca in an interview. The 16-member Duty Hours Task Force has been meeting since last July. New draft standards

The current ACGME standards are widely flouted. Findings from confidential surveys of residents have shown 'widespread falsification' by trainees of actual work hours.

are likely to be issued by late April, and will then be available for public comment for 45 days, he said.

At the briefing, Dr. Charles A. Czeisler, professor of sleep medicine at Harvard Medical School, Boston, said that the current ACGME standards are widely flouted. He said confidential surveys of residents have shown "widespread falsification" by trainees on their actual work hours. Dr. Nasca responded that his organization was an educational accreditor, "not an employment regulator."

Added Dr. Nasca, "Our goal is to ensure substantial compliance with the regulations."

There is a tension between the educational mission, safety, and other factors, acknowledged Dr. Nasca, adding that this is why the Duty Hours Task Force had gathered evidence and opinions from more than 140 organizations.

"There's a constant balance we have to take between setting realistic expectations for how residents are scheduled for duty and the expectations that programs comply with those, coupled with the desire to inculcate in physicians a sense of personal responsibility for the safety and care of each individual patient," said Dr. Nasca.

The risk of fatigue also has to be balanced against the risk of increased errors when patients are handed off to an increasing number of caregivers, he said. The evidence is conflicting on whether reduced work hours improves patient safety, added Dr. Nasca.

However, he said he welcomed the new group's attention to work hours. "This is an important issue for the public to understand," Dr. Nasca said. ■

BRIEF SUMMARY - Consult full prescribing information before use.

PENNSAID (didofenac sodium topical solution) 1.5% w/w is for topical use only. Initial U.S. Approval: 1988

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK

Cardiovascular Risk

- Nonsteroidal anti-inflammatory drugs (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 [see Warnings and Precautions (5.1)].
- PENNSAID is contraindicated in the perioperative setting of coronary artery bypass graft (CABG) surgery [see Contraindications (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 [see Warnings and Precautions (5.2)].

CONTRAINDICATIONS

PENNSAID is contraindicated in patients with a known hypersensitivity to didofenac sodium or any other component of PENNSAID.

PENNSAID is contraindicated in patients who have experienced asthma, urticaria, or 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 (5.7, 5.10)].

PENNSAID is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)].

WARNINGS AND PRECAUTIONS

Cardiovascular Thrombotic Events

Clinical trials of several oral 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 (MI), and stroke, which can be fatal. All NSAIDs, including PENNSAID and COX-2 selective and nonselective orally administered NSAIDs, 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 an orally administered COX-2 selective NSAID for the treatment of pain in the first 10 to 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 NSAIDs, such as didofenac, does increase the risk of serious GI events [see Warnings and Precautions (5.2)].

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

NSAIDs, including didofenac, 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 to 6 months, and in about 2 to 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 therapy is not without risk.

Prescribe NSAIDs, including PENNSAID, with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal 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 of 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, use special care when treating this population.

To minimize the potential risk for an adverse GI event, use the lowest effective dose for the shortest possible duration. Remain alert for signs and symptoms of GI ulceration and bleeding during didofenac therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, consider alternate therapies that do not involve NSAIDs.

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 oral didofenac-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 an oral didofenac-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 didofenac treatment (ALT was not measured in all studies).

In an open-label, controlled trial of 3,700 patients treated for 2 to 6 months, patients with oral didofenac 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 to 8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving didofenac 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 oral didofenac 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 oral didofenac associated drug-induced liver injury with current use compared with non-use of didofenac 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 didofenac, the adjusted odds ratio increased further with female gender, doses of 150 mg or more, and duration of use for more than 90 days.

Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with didofenac, 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, monitor transaminases within 4 to 8 weeks after initiating treatment with didofenac. However, severe hepatic reactions can occur at any time during treatment with didofenac. 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 PENNSAID 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 to take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver-related event in patients treated with PENNSAID, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing PENNSAID 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 PENNSAID.

Hypertension

NSAIDs, including didofenac, 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 PENNSAID, 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 treated with NSAIDs, including PENNSAID. Use PENNSAID with caution in patients with fluid retention or heart failure.

Renal Effects

Use caution when initiating treatment with PENNSAID 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 PENNSAID in patients with advanced renal disease. Therefore, treatment with PENNSAID is not recommended in patients with advanced renal disease. If PENNSAID therapy is initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to PENNSAID. Do not prescribe PENNSAID 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 (4) and Warnings and Precautions (5.10)]. Seek emergency help in cases where an anaphylactoid reaction occurs.

Skin Reactions

Do not apply PENNSAID to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug.

NSAIDs, including PENNSAID, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations, and discontinue use of the drug at the first appearance of skin rash or any other signs of hypersensitivity.

Pregnancy

PENNSAID should not be used by pregnant or nursing women or those intending to become pregnant.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, do not administer PENNSAID to patients with this form of aspirin sensitivity and use with caution in patients with preexisting asthma.

Sun Exposure

Instruct patients to avoid exposure to natural or artificial sunlight on treated knee(s) because studies in animals indicated topical didofenac treatment resulted in an earlier onset of ultraviolet light-induced skin tumors. The potential effects of PENNSAID on skin response to ultraviolet damage in humans are not known.

Eye Exposure

Avoid contact of PENNSAID with eyes and mucosa. Advise patients that if eye contact occurs, immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

Oral Nonsteroidal Anti-Inflammatory Drugs

Concomitant use of oral NSAIDs with PENNSAID resulted in a higher rate of rectal hemorrhage, more frequent abnormal creatinine, urea and hemoglobin. Therefore, do not use combination therapy with PENNSAID and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.

Corticosteroid Treatment

PENNSAID cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. For patients on prolonged corticosteroid therapy, taper slowly if a decision is made to discontinue corticosteroids.

Inflammation

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

Hematological Effects

The effects of PENNSAID on platelet function were studied in 10 healthy subjects administered 80 drops four times a day for 7 days. There was no significant change in platelet aggregation following one week of treatment [see Clinical Pharmacology (12.4)].

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect on erythropoiesis. Check hemoglobin or hematocrit of patients on PENNSAID if they exhibit any signs or symptoms of anemia or blood loss.

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

Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms in patients taking NSAIDs, monitor patients for signs or symptoms of GI bleeding. Check CBC and a chemistry profile periodically in patients on long-term treatment with NSAIDs. Discontinue PENNSAID if abnormal liver tests or renal tests persist or worsen.

ADVERSE REACTIONS

Clinical Studies Experience

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

The data described below reflect exposure to PENNSAID of 911 patients treated between 4 and 12 weeks (mean duration of 49 days) in seven Phase 3 controlled trials, as well as exposure of 793 patients treated in an open-label study, including 463 patients treated for at least 6 months, and 144 patients treated for at least 12 months. The population mean age was approximately 60 years; 89% of patients were Caucasians, 64% were females, and all patients had primary osteoarthritis. The most common adverse events with PENNSAID were application site skin reactions. These events were the most common reason for withdrawing from the studies.

Application site reactions:

In controlled trials, the most common treatment-related adverse events in patients receiving PENNSAID were application site skin reactions. Application site reactions were characterized by one or more of the following: dryness, erythema, induration, vesicles, pruritus, vasodilation, acne, and urticaria. The most frequent of these reactions were dry skin (32%), contact dermatitis characterized by skin erythema and induration (9%), contact dermatitis with vesicles (2%) and pruritus (4%). In one controlled trial, a higher rate of contact dermatitis with vesicles (4%) was observed after treatment of 152 subjects with the combination of PENNSAID and oral didofenac. In the open label uncontrolled long-term safety study, contact dermatitis occurred in 13% and contact dermatitis with vesicles in 10% of patients, generally within the first 6 months of exposure, leading to a withdrawal rate for an application site event of 14%.

Adverse events common to the NSAID class:

In controlled trials, subjects treated with PENNSAID experienced some adverse events associated with the NSAID class more frequently than subjects using placebo (constipation, diarrhea, dyspepsia, nausea, flatulence, abdominal pain, edema). The combination of PENNSAID and oral didofenac, compared to oral didofenac alone, resulted in a higher rate of rectal hemorrhage (3% vs. less than 1%), and more frequent abnormal creatinine (12% vs. 7%), urea (20% vs. 12%), and hemoglobin (13% vs. 9%), but no difference in elevation of liver transaminases.

The following adverse reactions occur in ≥2% of patients receiving PENNSAID, where the rate in the PENNSAID group exceeded placebo, from seven controlled studies conducted in patients with osteoarthritis. Since these trials were of different durations, these percentages do not capture cumulative rates of occurrence: Dry Skin (Application Site); Contact Dermatitis (Application Site); Dyspepsia; Abdominal Pain; Flatulence; Pruritus (Application Site); Diarrhea; Nausea; Pharyngitis; Constipation; Edema; Rash (Non-Application Site); Infection; Echinymosis; Dry Skin (Non-Application Site); Contact Dermatitis, vesicles (Application Site); Paresthesia (Non-Application Site); Accidental Injury; Pruritus (Non-Application Site); Sinusitis; Halitosis; and Application Site Reaction (not otherwise specified).

See the full prescribing information, Section 6.1 for a table showing the actual number of occurrences.

Postmarketing Experience

In non-US postmarketing surveillance, the following adverse reactions have been reported during post-approval use of PENNSAID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, body odor, chest pain, edema, face edema, halitosis, headache, lack of drug effect, neck rigidity, pain

Cardiovascular: palpitation, cardiovascular disorder

Digestive: diarrhea, dry mouth, dyspepsia, gastroenteritis, decreased appetite, mouth ulceration, nausea, rectal hemorrhage, ulcerative stomatitis

Metabolic and Nutritional:

creatinine increased

Musculoskeletal: leg cramps, myalgia

Nervous: depression, dizziness, drowsiness, lethargy, paresthesia, paresthesia at application site

Respiratory: asthma, dyspnea, laryngismus, laryngitis, pharyngitis

Skin and Appendages: At the Application Site: contact dermatitis, contact dermatitis with vesicles, dry skin, pruritus, rash; Other Skin and Appendages Adverse Reactions: eczema, rash, pruritus, skin discoloration, urticaria

Special Senses: abnormal vision, blurred vision, cataract, ear pain, eye disorder, eye pain, taste perversion

DRUG INTERACTIONS

Drug interactions with the use of PENNSAID have not been studied. The following drug interactions (Sections 7.1 to 7.7) are noted for oral didofenac sodium.

Aspirin

When didofenac is administered with aspirin, the binding of didofenac to protein is reduced, although the clearance of free didofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of didofenac 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 users of either drug alone.

ACE-inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. Consider this interaction in patients taking NSAIDs concomitantly with ACE-inhibitors.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. The response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe the patient 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 NSAIDs, including didofenac, 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 may indicate that they could enhance the toxicity of methotrexate. Use caution when NSAIDs, including didofenac, are administered concomitantly with methotrexate.

Cyclosporine

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

Oral Nonsteroidal Anti-Inflammatory Drugs

Concomitant use of oral NSAIDs with PENNSAID has been evaluated in one Phase 3 controlled trial and in combination with oral didofenac, compared to oral didofenac alone, resulted in a higher rate of rectal hemorrhage (3% vs. less than 1%), and more frequent abnormal creatinine (12% vs. 7%), urea (20% vs. 12%) and hemoglobin (13% vs. 9%). Therefore, do not use combination therapy with PENNSAID and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.

Topical treatments

Instruct patients that before applying sunscreen, insect repellent, lotion, moisturizer, cosmetics, or other topical medication to the same skin surface of the knee treated with PENNSAID, they must wait until the treated area is completely dry.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Teratogenic Effects:

There are no adequate and well-controlled studies of PENNSAID in pregnant women. PENNSAID should not be used by pregnant women as its safe use has not been adequately determined and starting at 30 weeks gestation, didofenac and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Developmental studies in animals demonstrated that didofenac sodium administration did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at doses up to 20 mg/kg/day (0.6-fold the maximum recommended human dose [MRHD] of 154 mg/day based on body surface area comparison), and in rats and rabbits at doses up to 100 mg/kg/day (approximately 0.6-fold and 1.3-fold the MRHD, respectively). Published reproductive and developmental studies of dimethyl sulfoxide (DMSO, the solvent used in PENNSAID) are equivocal as to potential teratogenicity.

Nonteratogenic Effects:

In rats, maternally toxic doses of didofenac were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.

Labor and Delivery

The effects of PENNSAID on labor and delivery in pregnant women are unknown. In rat studies maternal exposure to didofenac, as with other NSAID drugs, known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased offspring 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 didofenac 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 PENNSAID, 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.

Geriatric Use

Of the 911 patients treated with PENNSAID in seven controlled, Phase 3 clinical trials, 444 subjects were 65 years of age and over. There was no age-related difference in the incidence of adverse events. Of the 793 patients treated with PENNSAID in one open-labeled safety trial, 334 subjects were 65 years of age and over including 107 subjects 75 and over. There was no difference in the incidence of adverse events with long-term exposure to PENNSAID for this elderly population. As with any NSAID, use caution in treating the elderly (65 years and older) and it may be useful to monitor renal function since they are more likely to have decreased baseline renal function.

OVERDOSAGE

There have been no known experiences of overdose with PENNSAID.

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.

Manage patients using symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis is not recommended due to a possibility of aspiration and subsequent respiratory irritation by DMSO contained in PENNSAID. 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).

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