ARTHRITIS MARCH 2010 • RHEUMATOLOGY NEWS

Proinflammatory Cytokines May Predict RA Risk

BY AMY ROTHMAN SCHONFELD

levated concentrations of proinflammatory cytokines, cytokinerelated factors, and chemokines, indicating activation of the immune system, have been found in the blood of people years before they developed symptoms of rheumatoid arthritis that involved the joints, according to a report by Heidi Kokkonen and coinvestigators

at Umeå (Sweden) University. The study was published in the February 2010 issue of Arthritis and Rheumatism.

By comparing blood samples of people diagnosed with RA to normal controls and "prepatients" (those who go on to develop RA), investigators said that they hope the results will help predict an individual's risk of developing RA.

The investigators analyzed samples from the Medical Biobank of Northern Sweden, which invites all adult individuals from the county of Västerbotten to contribute blood samples. Within this population-based cohort, there were 86 individuals who went on develop inflammatory joint disease that fulfilled American College of Rheumatology classification criteria for RA after their donation of blood. For these prepatients, the median time predating the onset of symptoms was 3.3 years (range, 1.1-5

years). Of the 86 prepatients, 69 also provided blood samples at the time of RA diagnosis. For every prepatient, three control subjects were randomly selected from the Biobank register and matched for sex, age, and area of residence.

Several cytokines, cytokine-related factors, and chemokines were upregulated in prepatients, compared with controls. The greatest increases were noted for the Th2-related cytokines, eotaxin, and interleukin-4, with elevated levels also observed for Th1 cytokines, IL-12, interferon-gamma, and IL-10.

A multivariate classification algorithm known as the random forest method, similar to decision trees, was used to estimate which groups of cytokines, cytokine-related factors, or chemokines could best distinguish a particular group of patients. For prepatients, characteristic changes were related to both the Th1 and Th2 lineage, and to Treg cells, representing the adaptive immune system, the authors wrote. Elevation of IL-17 levels did not reach statistical significance.

Levels of at least two-thirds of the cytokines or cytokine-related factors were above the median values for control subjects in 50 of 85 prepatients.

Of the chemokines, MCP-1 and MIP-1 alpha levels were significantly increased in prepatients, compared with controls, as were the levels of granulocytemacrophage colony-stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF).

When the authors calculated the sensitivity and specificity of different factors for the development of RA in prepatients, they found that after anti-CCP antibodies and IgM rheumatoid factor (IgM-RF), eotaxin had the highest sensitivity (22.4%) and specificity (95.3%), with an odds ratio of 5.8. About one-half of the cytokines and cytokine-related factors that had significant predicative value for the development of RA in prepatients were related to Th1, Th2, and Treg cells. When all analyzed factors and anti-CCP antibodies were included, the sensitivity level rose to 51.2%, with a specificity of 91.9% for predicting the development of RA among prepatients and control subjects.

The factors distinguishing individuals before and after the onset of RA represented a more general immunologic response, as well as stromal cells and angiogenic factors. After RA diagnosis, significant increases were seen for most of the factors that were measured. IL-17 concentrations actually decreased after RA diagnosis. "This observation endorses the role of IL-17 in the initiating phase [of RA], and, as the pathogenesis progresses, other factors are subsequently brought into action," wrote the authors (Arthritis Rheum. 2010;62:383-91).

Although the authors were unable to conclude which agent initiates RA pathogenesis, they suggested that their findings present an opportunity for better predicting the risk of developing RA and intervening at an early stage to possibly prevent disease progression.

BRIEF SUMMARY - Consult full prescribing information before use.

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

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK Cardiovascular Risk

- PENNSAID is contraindicated in the perioperative setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4)].
- astrointestinal Risk
 INSAIDs 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
PENISAID is contraindicated in patients with a known hypersensitivity to diclofenac sodium or any other component of PENISAID.

Complores or Emission.

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

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

WARNINGS AND PRECAUTIONS
Cardiovascular Thrombotic Events
Clinical trials of several and CDM2-selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious candiovascular (CV) thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All KSAIDs, including PRINSAID and CDM2-selective and nonselective erally administered NSAIDs, may have a similar risk. Patients with known CV disease may be at greater risk. Io minimize the potential risk for an adverse CV event in patients treated with an ISAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain a left for the development of such events even in the abone of provious (C vomntons Inform In the control of the development of such events, even in the absence of previous VV 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 Controindications (4)).

and stoke (see Containdications (4)). There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with KSAID use. The concurrent use of aspirin and NSAIDs, such as dicidofenac, does increase the risk of serious GV events (see Winnings and Precautions (5.2)). Gastrointestinal Reffects — Risk of all Uteration, Beleding, and Perforation NSAIDs, including dicidofenac, can cause serious gastrointestinal (GI) adherse events including bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These evines adverse events can occur at any time, with or without varning symptoms, in patients treated with MSAIDs. Only one in five patients who develop a serious upper GI adherse event on MSAID therapy is symptomatic Upper GI ulcres, gross belieding, or perforation caused by MSAIDs cour 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 Inoper 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.

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Perscribe NSAID, including PENNISAID, 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 Gib bleed compared
to patients with neither of these risk factors. Other factors that increase the risk of lobelleding in patients
treated with NSAIDs include concentrate use of oral corticosteroids or anticoagulants, longer duration

- "Section is a "Section is a section of the control of the section of the useascumum nomus misuale consumiani use or oral corricosteroids 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.

ton 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 ulucration and bleeding during diclofenac 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.

risk patients, consider attentate therapies that do not unwolve NSAUIS.

Hepatic Effects

Borderline elevations (less than 3 times the upper limit of the normal [ULN] range) or greater elevations of transminanes courred in about 15% of and disclorear-texted patients in clinical trials of indications other than acute pain. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring

during diclofenac treatment (ALT was not measured in all studies).

aumg diodrenac treatment (ALI 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 diodrenac were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALI and/or ASI occurred in about 4% of the 3,700 patients and included marked elevations (-8 times the UIN) in about 1% of the 3,700 patients in this open-label study, a higher inclored borderline (less than 3 times the UIN), moderate (3 to 8 times the UIN), and marked (-8 times the UIN) elevations of ALI or ASI was observed in patients receiving diodrenac when compared to other MSADIs. Elevations in transaminases were seen more frequently in patients with osterarthrist 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 diclofenac in 42 of the 51 patie in all trials who developed marked transaminase elevations. In postmarketing reports, cases of dr n all trials who developed marked transaminase elevations. In postmarketing reports, cases of drug-nduced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of

In a European retrospective population-based, case-controlled study. 10 cases of oral diclofenac associate in a unique interospecture propusation tracesty, accordinates south, in class to an universities associated with a drug-induced liver injury with current use compared with non-use of diciofense, 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 diciofense, the adjusted odds ratio increased further with female gender, does of 150 mg or more, and duration of use for more then 90 days.

retines general, voices or Institute in the many in more, and unique on the cert in the large with discleract, Measure transminases (ALT and AST) periodically in patients receiving long-term therapy with discleract, 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 the contract of the second section of the contract trial data and postmarketing experiences, monitor transaminases within 4 to 8 weeks after initiating treatment with diddnean. However, severe hepatic reactions can cour at any time during treatment with diddnean. Lord severe severe hepatic reactions can cour at any time during treatment with diddnean. 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., essinophilia, rash, abdominal pain, diarrhea, dark time, etc.), disontinue PRINSAID immediately.

dark urine, etc.) discontinue PDNISAID immediately. On 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, puritus, jaundice, right tupper quadrant tendemess, and "fluilide" 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 drusp that are known to be potentially hepatotoxic (e.g. acetaminophen, certain antibiotics, antisplieptics). Caution patients to avoid taking unprescribed acetaminophen while using PENNSAID.

insulus, including activities(, an lead to new other or worsering to precessing injurieston), celler of which may contribute to the increased incidence of (Verents. Use ISAIDs, including PEMISAID) 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 ACC-inhibitors, thiazides or loop diuretics may have impaired response to these therapies when taking ISAIDs.

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.

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Renal Effects
Use caution when initiating treatment with PENNSAID in patients with considerable dehydr.

Use caution when initiating treatment with PLNNSJU in patients with considerable dehydration. Long-term administration of MSAIDs has resulted in renal papillary necosis 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 obse-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 Account neal fields in sextensive this Advanced result discontinuation.

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

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

Un this apply remission to operations morning, meaning and affect absorption and otherability of the distributions of matter absorption and otherability of the MISAIDs, including PRINSAID, and cause serious sind anderse events such as enfoliative dermaitis, Stevens Oshnison Syndrome (LSIS), and toxic epidemal neorolysis (TBN), which can be fatal. These serious event may occur without varaning, 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.

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. sensitive asthma has been associated with severe bounchospasm, 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 PENINSAID to patients with this form of aspirin sensitivity and use with caution in patients with preexisting asthma.

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

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Corticosteroid Treatment
FEINISAID Cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency, Ahrupt,
discontinuation of corticosteroids may lead to exacerbation of corticosteroid-response 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.

treatment fee Clinical Pharmacology (12-4).
Anemia is sometimes seen in patients receiving MSAIDs. This may be due to fluid retention, occult or gross Gl blood loss, or an incompletely described effect upon erythropoiesis. Check hemoglobin or hematorit of patients on PEMISAID if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs highligh platelet aggregation and have been shown to prolong bleeting time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration and reversible. Carefully monitor patients receiving PEMISAID who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

monuturing Because senious GI tract ulcerations and bleeding can occur without warning symptoms in patients taking IKSAIDs, 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

nou renect the rates observed in practice.

The data described below reflect exposure to PENISAID 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 12 months. The population mean age was approximately 60 years, 89% of patients were danales, and plaints had primary osterachtrist. The most common adverse events with PENISAID were application site skin reactions. These events were the most common reason for withdrawing from the studies.

tor windrawing from the studies. Application size reactions:

In controlled trials, the most common treatment-related adverse events in patients receiving PENNSAID were application site skin reactions. Application site reactions were donacterized by one or more of the following dryness; eypthema, industion, vesicles, parentise, purrutus, vasoidiation, acne, and urticania. The most frequent of these reactions were dry skin (32%), contact dermattist characterized by skin eypthema and industania (9%), contact dermatist with vesicles (2%) and purrutus (4%). In more controlled trial, a higher rate of contact dermatitis with vesicles (4%) was observed after treatment of 152 subjects with the combination of PENNSAID and and addiofenae. In the open label uncontrolled long-term safety study, contact demattitis occurred in 33% and contact demattist withvesice in 10% for platents, generally within the first of months of exposure, leading to a withdrawal rate for an application site event of 14%. Adverse exests commons to the NSAID descriptions.

study, characterimination of exposing, leading to a withdrawal rate for an application site event of 14%.

**Adverse events ammon to the INSAID class:*
In controlled trials, subjects treated with PENISAID experienced some adverse events associated with the INSAID class more frequently than subjects using placebo (constipation, diarrhea, dyspepsia, nausea, flatulence, abdominal pain, edema). The combination of PENISAID and oral diclofenac, compared to oral diclofenac, compared to oral diclofenac, compared to oral diclofenac, compared to oral diclofenac alone, resulted in a higher rate of rectal hemorthage (35 vs. Jess Ishan 19s), and more frequent abnormal creathine (128 vs. 786), urea (20% vs. 1296), and hemoglobion (13% vs. 5%), but no difference in elevation of liver transaminases.

The following adverse reactions occur in ≥1% of patients receiving PENISAID, where the rate in the PENISAID 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); Contact Dermatitis (Application Site), Contact Dermatitis, vs. Pensyngitis, Constitution Site), Farsthesia (Mon-Application Site), Contact Dermatitis, vs. Pensiberation, Pacification Site), Parsthesia (Mon-Application Site), Contact Dermatitis, vs. Pensyngitis, Constitution (Non-Application Site), Faltencis; and Application Site), Stantista (Mon-Application Site), Faltencis; and Application Site), Section 6.1 for a table showing the actual number of occurrences.

Postmarketing Experience

Postmarketing Experience
In non-US postmarketing surveillance, the following adverse reactions have been reported during post-approval use of PENISAID. 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

reasonsimp to drug exposure.

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

Gardowscular palpitation, cardiovascular disorder

(Bigestive: diarrhea, dry mouth, dyspepsia, gastroententis, decreased appetite, mouth ulceration, nausea, retal hemorrhage, ulcerative stomatics.

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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

in and Appendages: At the Application Site: contact dermatitis, contact dermatitis with vesicles, y skin, pruritus, rash; *Other Skin and Appendages Adverse Reactions*: eczema, rash, pruritus, skin

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

DRUG INTERACTIONS
Drug interactions with the use of PENINSAID have not been studied. The following drug interactions [sections 7.1 to 7.7] are noted for oral diclofenac sodium.

Aspirin
When didolenac is administered with aspirin, the binding of diclofenac to protein is reduced, although
the deaance of free diclofenac is not altered. The clinical significance of this interaction is not known;
however, as with other NSAIDs, concomitant administration of diclofenac 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.

ALE-INIDITORS

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors.

Consider this interaction in patients taking NSAIDs concomitantly with ACE-inhibitors.

Direction (Initial studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of funcemide 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 Wornings and Precautions (5.6)], as well as to assure disurctic efficacy.

Unumum. Its Mum and 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 IKSAID. Thus, when IKSAIDs, including dicidenac, and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity. Methotrexate

ISAIDs 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
diclofenac, are administered concomitantly with methotrexate.

when dicloteract is administered concomitantly with cyclosporne.

Oral Nonsteroidal Anti-Inflammatory Drugs
Concomitant use of oral NSAIDs with PENISAID has been evaluated in one Phase 3 controlled trial and in combination with oral diclofenac, compared to oral diclofenac 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 PENISAID and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.

treated area is completely dry.

USE IN SPECIFIC POPULATIONS

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

Tendangeric 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 straining at 30 weeks pestation, diclofferact and other ISABIO should be awided by pregnant women as premature dosure of the ductus arterious in the fetus may occur. Developmental studies in animals demonstrated that dicloffena sodium administration did not produce teratopenicity despet the induction of maternal toxicity and fetal toxicity in mite at doses up to 20 mg/day (0.6-fold the maximum recommended human dose up to 10 mg/a/day laces on body surface area comparison), and in rate and rabibits at doses up to 10 mg/a/day laces on body surface area comparison), and in rate and rabibits at doses up to 10 mg/a/day laces on body surface area comparison), and in rate studies of dimethyl sulfoxide (0MSO), the solvent used in PENNSAID) are equivocal as to potential teratogenicity.

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

Labor and Delivery

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

Musting Mothers:

It is not known whether this drug is excreted in human milk, however, there is a case report in the literature indicating that dicoferac can be detected at low levels inbreast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PSINSAID, 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 One of 1) patients treated with removalum is event children, in the incidence of adverse events. Of the 799 patients treated with PBNISAID in one open-labeled sifereince in the incidence of adverse events. Of the 790 patients treated with PBNISAID in one open-labeled safety trial, 334 subjects were 65 years of age and over Incidual of 50 subjects 75 and over. There was no difference in the incidence of adverse events with long-term exposure to PENISAID 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 HSABID 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 MSAIDs, and may occur

following an overdose.

Manage patients using symptomatic and supportive care following an NSAID overdose. There are no specific anidotaes, Emeris is not recommended due to a possibility of a spiration 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 injection with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization 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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