Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in controlling pain in patients with arthritis; however, these agents are associated with a variety of adverse effects, with gastrointestinal (GI) toxicity being the most common.

### NSAID-related Gastrointestinal Toxicity

**Epidemiology**

The adverse reactions associated with NSAIDs vary in both incidence and severity. Approximately 10% to 20% of patients taking NSAIDs will develop dyspepsia, although the prevalence of this adverse event has been reported to be as high as 50%. Data have shown that dyspepsia results in 5% to 15% of patients discontinuing therapy within a 6-month period of initiating therapy. In addition, patients receiving NSAID therapy are at a 2.5- to 5-fold increased risk for serious GI complications compared with patients not taking NSAIDs. An estimated 100,000 hospital admissions and 7,000 to 10,000 deaths annually in the United States have been attributed to NSAID-related GI toxicity.

**Complications**

Both upper and lower GI complications can occur with NSAID therapy. Upper GI problems can range from asymptomatic mucosal damage, mild dyspepsia, nausea/vomiting, and abdominal pain to more serious complications such as peptic ulcers and bleeding. The frequency of dyspepsia is estimated to be doubled in NSAID users compared with non-users; however, the presence of dyspeptic symptoms does not always correlate with the development of more serious GI complications. Many patients with bleeding peptic ulcers have few symptoms prior to the event. Lower GI complications include mucosal inflammation and increased mucosal permeability, ulcerations, strictures, hemorrhage, perforation, and exacerbation of inflammatory bowel disease. Recent data have shown that lower GI adverse events are becoming more common in NSAID users, and these events are associated with higher mortality and more prolonged hospitalizations compared with upper GI events.

**Pathophysiology**

Injury to the GI tract by NSAIDs is thought to be multifactorial and related to the direct toxic effects of NSAIDs on the mucosa and to systemic effects resulting from inhibition of cyclooxygenase-1 (COX-1) and thromboxane A2. Direct topical toxicity occurs as a result of the acidic properties of aspirin and many other NSAIDs. These agents are ingested and remain in their non-ionized, lipophilic form in the highly acidic gastric lumen, which enables NSAIDs to penetrate through the gastric mucus, across plasma membranes, and into epithelial cells. Once in epithelial cells, NSAIDs are dissociated to their ionized state, resulting in trapping of hydrogen ions and, ultimately, damage to the GI mucosa.

By inhibiting COX-1, nonselective NSAID use results in decreased synthesis of protective mucosal prostaglandins. This is the reason why selective COX-2 inhibitors seem to be associated with a lower risk for peptic ulcers. In addition, NSAIDs inhibit thromboxane A2, which reduces platelet function and results in a higher risk for bleeding. Data also suggest that NSAIDs impair angiogenesis, which is the growth of new capillary blood vessels and an important natural process in healing and reproduction, and this interference may affect ulcer healing.

**Risk Factors**

Numerous risk factors have been identified that place patients at increased risk for NSAID-related GI complications. A publication by the Practice Parameters Committee of the American College of Gastroenterology (ACG) guidelines on the Prevention of NSAID-related Ulcer Complications, states that risk factors for NSAID-related GI complications include a previous GI event, especially if the event was a previous complicated ulcer; older age; concomitant use of anti-coagulants, corticosteroids, or other NSAIDs including low-dose aspirin; use of high-dose NSAIDs; and chronic debilitating disorders. The risk for GI complications appears to increase linearly with age, with patients over 70 years old having a risk similar to those with a previous history of an ulcer. The guidelines also state that the presence of Helicobacter pylori is an independent and additive risk factor for NSAID-related GI toxicity. Other risk factors for GI toxicity include alcohol use and smoking.

The guidelines classify patients as being at high, moderate, or low risk for NSAID-related GI complications (Table 1). Preventive strategies are tailored to the individual patient's GI risk and will be discussed below.

**FDA Warning**

The occurrence of NSAID-related GI toxicity prompted the FDA to review postmarketing adverse event reports to determine if new labeling requirements were needed for over-the-counter (OTC) NSAID products. Based on the data, the FDA concluded that serious stomach bleeding events can occur when NSAIDs are used according to the current warnings and directions on the OTC label. The review noted the various risk factors for NSAID-related GI toxicity discussed above and determined that these risk factors should be prominently displayed on the packaging of OTC NSAIDs.

In April 2009, the FDA published a

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**Managing GI Issues**

**In the Rheumatology Patient on Chronic NSAID Therapy**

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final rule requiring manufacturers of OTC NSAIDs (including but not limited to aspirin, carbamazepine calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen, and sodium salicylate) to revise their labeling to contain new GI warnings so that patients are aware of the potential risks associated with use of these medications. An overview of the GI-related labeling changes for OTC NSAIDs is provided in Table 2.

**Guidelines for Prevention**

The ACG guidelines on the prevention of NSAID-related ulcer complications discuss 2 methods that are commonly used to prevent the development of peptic ulceration and mucosal injury in patients taking NSAIDs: 1) cotherapy with misoprostol, a high-dose histamine 2-receptor antagonist (H₂RA), or a proton-pump inhibitor (PPI); or 2) use of a COX-2-selective NSAID instead of a traditional, nonselective NSAID. The guidelines specifically state that use of enteric-coated or buffered NSAIDs or cotherapy with sucralfate have not been shown to be effective in preventing NSAID-related GI toxicity.

**Misoprostol Cotherapy**

Misoprostol, a synthetic prostaglandin E₁ analog, was one of the first agents approved for the prevention of NSAID-related ulceration. Data from a large randomized, 6-month trial involving 8,843 patients receiving continuous NSAID therapy for the treatment of rheumatoid arthritis showed that use of misoprostol 200 mcg 4 times daily reduced the risk for serious upper GI complications by 40% compared with placebo. A 2002 Cochrane review of 4 randomized controlled trials evaluating the prevention of NSAID-induced gastroduodenal ulcers concluded that misoprostol significantly reduced the risk for endoscopic gastric and duodenal ulcers, with an 800-mcg per day dose being more effective than a 400-mcg per day dose. Misoprostol 800 mcg per day was associated with a relative risk (RR) for endoscopic ulcers of 0.18 (95% confidence interval [CI], 0.12-0.27) compared with placebo, and the 400 mcg per day dose was associated with a RR of endoscopic ulcers of 0.43 (95% CI, 0.28-0.67) compared with placebo. However, use of this agent was associated with diarrhea at both doses (800 mcg per day: RR, 3.16 [95% CI, 2.33-4.29] and 400 mcg per day: RR, 1.76 [95% CI, 1.37-2.26]). The guidelines state that misoprostol, when given in full doses (800 mcg per day), is very effective in preventing ulcers and ulcer complications in patients taking NSAIDs; however, the usefulness of this agent is limited by adverse effects such as diarrhea (occurring in 13% of patients) and abdominal pain (occurring in 7% of patients), and adherence issues related to the 4-times-daily dosing requirement.

High-dose H₂RA is defined as a double dose of therapy (eg, famotidine 40 mg twice daily) and has been shown to be effective in reducing the risk for NSAID-induced ulcers. The 2002 Cochrane review concluded that high-dose H₂RA therapy was associated with a significant reduction in the risk for both duodenal (RR, 0.26; 95% CI, 0.11-0.65) and gastric (RR, 0.44; 95% CI, 0.26-0.74) ulcers compared with placebo. The guidelines state that high-dose H₂RA therapy is superior to placebo in reducing the risk for NSAID-induced endoscopic peptic ulcers; however, it is significantly less effective than combination therapy with PPIs.

**Combination Therapy**

Combination therapy with an NSAID and PPI for NSAID-related upper GI injury prophylaxis and treatment has skyrocketed in recent years. The increased use of this combination has been attributed to a multitude of published literature supporting the efficacy and safety of this combination. Data from 2 large randomized, 6-month controlled trials performed in patients with osteoarthritis and rheumatoid arthritis who had ulcers that exceeded 3 mm in diameter or more than 10 erosions showed that omeprazole cotherapy resulted in better treatment outcomes compared with ranitidine and misoprostol. One study showed that after 8 weeks of treatment, 80% of patients given omeprazole 20 mg per day and 79% of those given omeprazole 40 mg per day were classified as having successful treatment, defined as the resolution of ulcer and the presence of fewer than 5 erosions in the stomach and duodenum, compared with 63% of patients given ranitidine (P<0.001 for omeprazole 20 mg per day; P=0.001 for omeprazole 40 mg per day). The second study showed that after 8 weeks of treatment, healing of gastric ulcers was significantly more common among patients given omeprazole 20 mg per day (87%) compared with those given misoprostol (73%; P<0.004). The guidelines state that PPIs significantly reduce gastric and duodenal ulcers and their complications in patients taking nonselective NSAIDs or COX-2 inhibitors.

Although the efficacy of PPIs has been established, these agents have been associated with some key adverse events and drug–drug interactions. Data suggest that PPIs may increase the risk for Clostridium difficile–associated disease, and long-term PPI use may increase the risk for hip fracture. Data from a retrospective case-control study of 188 hospitalized patients reported that patients using PPIs were 3.6 times more likely to develop C. difficile–associated diarrhea. Another case-control study reported that exposure to PPIs for 7 years or more increased the risk for an osteoporosis-related fracture by 1.92 times, with the risk for hip fracture increasing 4.55 times after 7 years of exposure. In addition, PPI use has been linked to community-acquired pneumonia (CAP). A nested case-control study reported that PPI therapy started within 30 days was associated with an increased risk for CAP. Unfortunately, the incidence of these 3 adverse events is difficult to quantify, because the occurrence varies between studies.

Recently, there has been concern over whether PPIs given in combination with clopidogrel decrease the antiplatelet efficacy of the drug. Data from a nested case-control study of 13,636 patients prescribed clopidogrel following an acute myocardial infarction showed that concomitant therapy with a PPI, other than pantoprazole, was associated with loss of the beneficial effects of clopidogrel. Another study confirmed that pantoprazole does not appear to alter the effectiveness of clopidogrel compared with other PPIs such as omeprazole or esomeprazole. The FDA issued an alert in November 2009 warning clinicians that the combination of omeprazole and clopidogrel should be avoided because omeprazole inhibits cytochrome P450 (CYP) 2C19, which is responsible for the conversion of

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**Table 1. Risk Factors for NSAID-related GI Toxicity**

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Risk factor</th>
</tr>
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<tbody>
<tr>
<td>High risk</td>
<td>History of a previously complicated ulcer, especially a recent flare-up.</td>
</tr>
<tr>
<td></td>
<td>More than 2 risk factors</td>
</tr>
<tr>
<td>Moderate risk (1 to 2 risk factors)</td>
<td>Age &gt;65 y</td>
</tr>
<tr>
<td></td>
<td>High-dose NSAID therapy</td>
</tr>
<tr>
<td></td>
<td>History of uncomplicated ulcer</td>
</tr>
<tr>
<td></td>
<td>Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants</td>
</tr>
<tr>
<td>Low risk</td>
<td>No risk factors</td>
</tr>
</tbody>
</table>

* H. pylori is an independent risk factor and needs to be addressed separately. NSAID, nonsteroidal anti-inflammatory drug

Adapted from reference 2.

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**Table 2. GI-related Labeling Changes for OTC NSAIDs**

- The ingredient name and the term NSAID must be highlighted or in bold type and in a prominent print size on the principal display panel.
- The following warnings must be present for products indicated for adults:
  - Stomach bleeding warning (in bold): This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause severe stomach bleeding. The chance is higher if you are 60 or older, have had stomach ulcers or bleeding problems, take a blood thinning (anticoagulant) or steroid drug, take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others), have 3 or more alcoholic drinks every day while using this product, or take more or for a longer time than directed.
  - Ask a doctor before use if stomach bleeding warning applies to you, you have a history of NSAID-induced bleeding problems, take blood thinning (anticoagulant) or steroid drug, have high blood pressure, heart disease, liver cirrhosis, or kidney disease, or you are taking a diuretic.
  - Stop use and ask a doctor if you experience any of the following signs of stomach bleeding: feel faint, vomit blood, have bloody or black stools, or have a stomach pain that does not get better.

Adapted from references 7, 8.

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* Slightly different labeling requirements apply to products only labeled for children under 12 years of age and those for both adults and children.
GI ISSUES continued from page 33

clopidogrel to its active form. The FDA went on to recommend avoidance of esomeprazole and clopidogrel as well, and stated that separating the intake of these PPIs from clopidogrel would not decrease the likelihood of this interaction. Acid-suppressing agents such as ranitidine, famotidine, nizatidine, and antacids do not appear to interfere with clopidogrel metabolism and are good alternatives for these patients.

When considering use of a COX-2 inhibitor, the ACG guidelines state that these agents are associated with a significantly lower incidence of gastric and duodenal ulcers compared with nonselective NSAIDs; however, this beneficial effect is lost in patients who are more likely taking low-dose aspirin therapy. In addition, COX-2 inhibitors have been linked to serious cardiovascular adverse events, which limits their usefulness. However, ACG acknowledges that emerging evidence suggests that both COX-2 inhibitors and nonselective NSAIDs, with the possible exception of naproxen, increase the risk for cardiovascular adverse events. The ACG guidelines state that the lowest possible dose of celecoxib should be used to minimize potential cardiovascular adverse events.

Based on a patient’s GI and cardiovascular risk factors, ACG has published specific recommendations for the prevention of NSAID-related ulcer complications (Table 3). The guidelines state that all patients who are about to start long-term nonselective NSAID therapy should be considered for testing for H. pylori and treated if it is present.

**New Combination Agents**

In April 2010, the FDA approved a new combination extended-release tablet that contains enteric-coated naproxen and esomeprazole (Vimovo, AstraZeneca and POZEN) for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and to decrease the risk for gastric ulcers in patients at risk for NSAID-associated gastric ulcers. The tablets will be marketed in 2 strengths of 375 mg/20 mg and 500 mg/20 mg of naproxen/esomeprazole, and the dose is 1 tablet twice daily taken 30 minutes before meals. The tablet has a unique release mechanism and is considered to be delayed-release. The core of the tablet contains enteric-coated naproxen, which is surrounded by immediate-release esomeprazole; because of the release mechanism, the tablet must be swallowed whole and cannot be crushed or chewed. Data from 2 studies which compared naproxen/esomeprazole 500 mg/20 mg with enteric-coated naproxen 500 mg have been published together in *Alimentary Pharmacology and Therapeutics.* Both Phase III trials had identical methods: randomized, controlled, double-blind, parallel-group, multicenter studies conducted in the United States. The objective was to determine if the combination of esomeprazole and naproxen (Vimovo) reduced the risk for gastric ulcers at 6 months compared with enteric-coated naproxen without gastroprotection. To participate in the studies, patients had to have at least 6 months of daily NSAID therapy and have a risk factor for a GI complication. Qualifying risk factors included age 50 years or older or at least 18 years old with a history of an uncomplicated gastric or duodenal ulcer within the previous 5 years. Before randomization, patients were stratified according to the use of low-dose aspirin; treatment regimens for both trials included naproxen 500 mg (n=216, n=210) or naproxen/esomeprazole 500 mg/20 mg (n=218, n=210). Naproxen was enteric-coated, and treatments were given twice daily for 6 months or until development of a gastric ulcer. Patients were allowed to take acetaminophen as needed for pain and an antacid for GI discomfort. The primary end point was cumulative incidence of gastric ulcers at months 1, 3, and 6 as assessed by endoscopy. Secondary end points included onset of duodenal ulcer, NSAID-associated upper GI events, number of patients discontinuing treatment due to a GI event, and discontinuation due to an adverse event. A variety of symptom questionnaires were also administered.

Demographic data revealed that a majority of patients were female with a mean age of 61 years. The most common indication for NSAID therapy was osteoarthritis (80%), and less than one-fourth of patients were receiving low-dose aspirin therapy. The cumulative incidence of gastric ulcers over 6 months in the intent-to-treat population was significantly lower with combination therapy (4.1% vs 23.1% and 7.1% vs 24.3% for study 1 and study 2, respectively; P<0.001 for both). Patients taking low-dose aspirin at baseline had results that were similar to the overall population, with 3% of those who received combination therapy experiencing an ulcer compared with 28.4% of those receiving naproxen (P<0.001). The overall incidence of duodenal ulcers was also significantly lower with combination therapy (0.5% vs 5.1% in study 1 [P=0.003] and 1% vs 5.7% in study 2 [P=0.007]).

The most common NSAID-associated upper GI events were erosive gastritis, gastritis, dyspepsia, and erosive duodenitis; these events occurred more frequently in naproxen recipients (69% vs 52.3% and 71.9% vs 54.3% for study 1 and study 2, respectively; P<0.001 for both). More patients receiving naproxen alone discontinued therapy due to these events (12% vs 3.2% in study 1 [P<0.001] and 11.9% vs 4.8% in study 2 [P=0.009]). Patient-reported upper GI tolerability (as assessed by surveys) was better with combination therapy. No significant differences were found between regimens in terms of adverse effects. The authors concluded that the combination of naproxen and esomeprazole was superior to enteric-coated naproxen alone for reducing the incidence of gastric ulcers in at-risk patients requiring long-term NSAID therapy.

A second combination agent (HZT-501) containing ibuprofen 800 mg and famotidine 26.6 mg is under investigation by Horizon Therapeutics. A decision on approval by the FDA is anticipated in the first quarter of 2011. Efficacy of HZT-501 was demonstrated in 2 identically designed Phase III trials known as Registration Endoscopic Study to Determine Ulcer Formation of HZT-501 Compared to Ibuprofen: Efficacy and Safety Study (REDUCE-1 and REDUCE-2). The trials have not been published as of June 2010; however, some details are available. The randomized, double-blind, controlled trials were designed to compare the efficacy of the combination product given 3 times daily for 24 weeks in reducing the incidence of gastric ulcers compared with ibuprofen 800 mg given 3 times daily. The second trial, REDUCE-2, expanded the primary outcome to include the incidence of duodenal ulcers. A total of 1,382 patients participated in the trials. Results revealed that

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**Table 3. Recommendations for Prevention of NSAID-related Ulcer Complications**

<table>
<thead>
<tr>
<th>Gastrointestinal Risk</th>
<th>Low CV risk</th>
<th>Moderate CV risk</th>
<th>High CV risk</th>
<th>Alternative therapy if possible OR COX-2 inhibitor + PPI or misoprostol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>NSAID alone</td>
<td>NSAID + PPI or misoprostol</td>
<td>High CV risk*</td>
<td>Naproxen + PPI or misoprostol</td>
</tr>
</tbody>
</table>

* Arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events.

**Table 4. Tips for Counseling Patients Using NSAIDs**

- Give patients examples of drugs that are NSAIDs and tell them that these agents are also found in a variety of medications, so read labels carefully.
- Tell patients that taking a higher dose than recommended of an NSAID can cause stomach bleeding, and the risk for this adverse event is increased in specific patients.
- Educate patients about potential signs and symptoms of stomach bleeding.
- Tell patients that taking a higher dose of an NSAID than recommended can also cause reversible kidney damage, and the risk for this adverse event is increased in patients who are over 60 years old; those with hypertension, heart disease, or pre-existing kidney disease; and those taking a diuretic.

Adapted from reference 2.
GI ISSUES
continued from page 34
the combination product was superior to ibuprofen in reducing the incidence of gastric ulcers (REDUCE-1: 12.9% vs 25.3%; P<0.05) and the incidence of gastric and duodenal ulcers (REDUCE-2: 13.8% vs 22.6%; P<0.05).
In addition to the Phase III data, an open-label safety study of the agent is currently recruiting.26 Publication of these trials will provide insight into the role of combination ibuprofen and famotidine in therapy.

Poor Prescribing Patterns
Although concomitant use of gastroprotective agents is recommended for patients taking NSAIDs who are at moderate to high risk for GI events, a multitude of data have shown that few patients are prescribed these agents.27-29 A prospective drug utilization study conducted at an orthopedic outpatient unit showed that out of 884 NSAID prescriptions, only 288 (32.6%) were co-prescribed with gastroprotective agents.27 Another study assessing time trends in preventive strategies among 50,126 NSAID users, of which 43.3% had at least 1 risk factor for an NSAID-related GI complication, showed that approximately 60% of new NSAID users with at least 1 risk factor and 52% of patients with a medical history of an upper GI event were not prescribed a proper preventive strategy.28 A 3-month, retrospective study of 338 patients discharged from an urban hospital on NSAID therapy showed that only 45.6% received any form of gastroprotection.29 These data show that prescribing patterns for gastroprotective agents are poor, and that the use of cotherapy in patients on NSAIDs needs improvement.

Physician, Patient Education Needed
Both prescribers of NSAID therapy and patients need to be educated about the GI risks associated with use of these agents. Physician education is needed to improve the poor prescribing rates for recommended gastroprotective cotherapies. Data have shown that physician education in combination with an electronic computer alert system informing...
Prescribers about the current recommended preventive strategies increases the use of gastroprotection among NSAID users.\(^{30}\) A study showed that use of gastroprotection increased from 43% to 61% when an electronic computer alert and physician education were implemented at a hospital (P < 0.001), and this rate increased even more in PPI-naive patients (from 26% to 55%; P < 0.0001).

Physicians need to be educated about the safety and effectiveness of gastroprotective therapies in patients receiving chronic NSAID therapy. It has been estimated that patients with one or more risk factors for upper GI complications receive no gastroprotection regimen 70% to 80% of the time.\(^{30}\) Therefore, pharmacists should strive to educate physicians on the risk factors for NSAID-induced gastroduodenal ulcers and the role of prophylactic therapies. In addition, pharmacists should educate physicians about the availability of new agents that have combined a nonselective NSAID with a PPI or H₂RA, because these agents may offer a more convenient dosing option for patients.

For patients, the American Gastroenterological Association Institute and Horizon Therapeutics have partnered and developed a Web site known as Connect to Protect (www.connecttoprotect.com), which educates patients about the GI risks associated with NSAIDs and how to manage those risks.\(^{31}\) Specific patient-related materials on the Web site include a discussion guide to help patients track their potential risks and prepare to discuss those risks with their physician, a dictionary of terms commonly used in diagnosing and treating NSAID-induced GI issues, and a patient narrative detailing first-hand experience of complications from chronic NSAID use. The Web site also contains tools for physicians such as a discussion guide, references on this topic, and a webinar program.

The FDA has also published Guide to Safe Use of Pain Medicine, which is available on the agency’s consumer health information Web page (www.fda.gov/ForConsumers).\(^{32}\) The document includes numerous tips for counseling patients to safely use NSAIDs (Table 4).

**Conclusion**

NSAID-related GI toxicity is an increasing problem and results in 100,000 hospital admissions and 7,000 to 10,000 deaths annually in the United States.\(^{2}\) The 2009 ACG guidelines on the prevention of NSAID-related ulcer complications were designed to give clinicians specific recommendations on the use of appropriate gastroprotective agents in patients receiving NSAIDs, with the goal of reducing the substantial burden associated with NSAID-related GI effects. Unfortunately, many studies have shown that clinicians are failing to follow these recommendations, and many patients at risk for NSAID-related GI effects are not receiving appropriate gastroprotective agents.\(^{27–29}\) Therefore, prescribers need to be educated about the occurrence of NSAID-related GI complications, which patients are at the greatest risk for these potential adverse events, and about the availability of new agents that have combined a nonselective NSAID with a PPI or H₂RA. In addition, patients need to understand their potential risks for NSAID-related GI adverse events, signs and symptoms of these events, and the proper steps to take if these events occur. Pharmacists can educate patients about the Connect to Protect Web site and the availability of materials on this topic on the FDA consumer Web site.

**References**


GI ISSUES
continued from page 37

7. Food and Drug Administration. Questions and answers on final rule on labeling changes to over-the-counter pain relievers.